



(19)

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 221 982 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
20.07.2005 Bulletin 2005/29

(51) Int Cl.⁷: **A61L 2/08, A61L 2/10,
C07D 475/14**

(21) Application number: **00965012.8**

(86) International application number:
PCT/US2000/025213

(22) Date of filing: **15.09.2000**

(87) International publication number:
WO 2001/028599 (26.04.2001 Gazette 2001/17)

(54) ISOALLOXAZINE DERIVATIVES TO NEUTRALIZE BIOLOGICAL CONTAMINANTS

ISOALLOXAZINDERIVATE ZUR NEUTRALISIERUNG VON BIOLOGISCHEN SCHMUTZSTOFFEN
DERIVES ISOALLOXAZINES PERMETTANT DE NEUTRALISER DES CONTAMINANTS
BIOLOGIQUES

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

- GOODRICH, Raymond, Paul, Jr.**
Colorado, 80227 (US)

(30) Priority: **19.10.1999 US 420652**

(74) Representative: **Cresswell, Thomas Anthony et al**
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(43) Date of publication of application:
17.07.2002 Bulletin 2002/29

(56) References cited:
EP-A-0 196 515 EP-A-0 679 398
WO-A-00/04930 WO-A-96/39816

(73) Proprietor: **Gambro, Inc.**
Lakewood Colorado 80215 (US)

(72) Inventors:

- PLATZ, Matthew, Stewart**
Columbus, OH 43235 (US)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

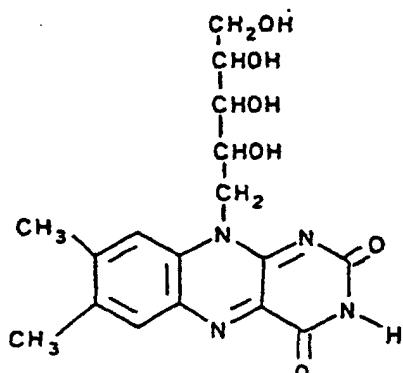
[0001] Contamination of blood supplies with infectious microorganisms such as HIV, hepatitis and other viruses and bacteria presents a serious health hazard for those who must receive transfusions of whole blood or administration of various blood components such as platelets, red cells, blood plasma, Factor VIII, plasminogen, fibronectin, anti-thrombin III, cryoprecipitate, human plasma protein fraction, albumin, immune serum globulin, prothrombin complex plasma growth hormones, and other components isolated from blood. Blood screening procedures currently available may miss contaminants. Thus, there is a need for sterilization procedures that effectively neutralize all infectious viruses and other microorganisms but do not damage cellular blood components, do not degrade desired biological activities of proteins, and preferably do not need to be removed prior to administration of the blood product to the patient.

[0002] The use of photosensitizers, compounds which absorb light of a defined wavelength and transfer the absorbed energy to an energy acceptor, has been proposed for blood component sterilization. Various photosensitizers have been proposed for use as blood additives. A review of some photosensitizers including psoralens, and some of the issues of importance in choosing photosensitizers for decontamination of blood products is provided in Goodrich, R. P., et al. (1997), "The Design and Development of Selective, Photoactivated Drugs for Sterilization of Blood Products," *Drugs of the Future* 22:159-171.

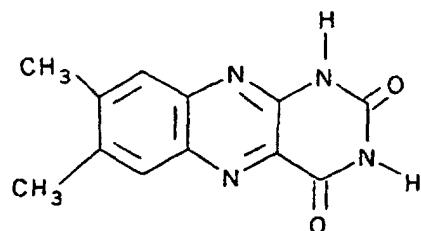
[0003] Some photosensitizers that have been proposed for use for blood component sterilization have undesirable properties. For example, European Patent Application 196,515 published October 8, 1986, suggests the use of non-endogenous photosensitizers such as porphyrins, psoralens, acridine, toluidines, flavine (acriflavine hydrochloride), phenothiazine derivatives, and dyes such as neutral red and methylene blue, as blood additives. Another molecule, chlorpromazine, has been used as a photosensitizer, however its usefulness is limited by the fact that it should be removed from any fluid administered to a patient after the decontamination procedure because it has a sedative effect. Protoporphyrin, which occurs naturally within the body, can be metabolized to form a photosensitizer, however, its usefulness is limited in that it degrades the desired biological activities of proteins.

[0004] In addition to molecules which can serve as photosensitizers, alkylating agents have been proposed for use as blood contaminant neutralizers. Alkylating agents are believed to deactivate microorganisms by alkylating nucleophilic groups of amino acid residues and nucleic bases at a certain pH. Ethyleneimine has been reported to deactivate certain viruses (United States Patent No. 5,891,075 (Budowsky, et al.), WO 97/07674 (published March 6, 1997)).

[0005] United States Patent Application Number 09/119,666 and continuation in part 09/357,188, describes methods and apparatus for neutralization of biological contaminants using endogenous photosensitizers, including 7,8-dimethyl-10-ribityl isoalloxazine (riboflavine).

**7,8-dimethyl-10-ribityl isoalloxazine**

[0006] 7,8-dimethyl-10-ribityl isoalloxazine (Riboflavin or vitamin B2) absorbs light from about 200 to 500 nm. The ring system core of 7,8-dimethyl-10-ribityl isoalloxazine is resistant to photodegradation but the ribityl side chain of riboflavin undergoes photodegradation. Photolysis of 7,8-dimethyl-10-ribityl isoalloxazine may form lumichrome (7,8-dimethylalloxazine) depending on conditions. 7,8-dimethylalloxazine strongly absorbs ultraviolet (UV) light and only weakly absorbs visible light.

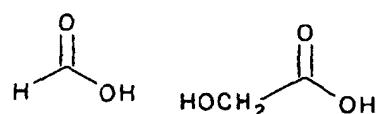


10

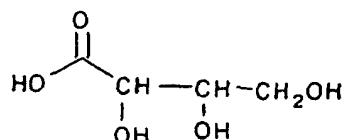
7,8-dimethylalloxazine

- 15 [0007] United States Patent No. 5,811,144 discusses the treatment of beer with visible light under substantially anaerobic conditions to reportedly reduce the riboflavin content of the beer.
- [0008] Small molecules such as those shown below which are derived from the ribityl side chain are expected to be products from the photolysis of riboflavin.

20

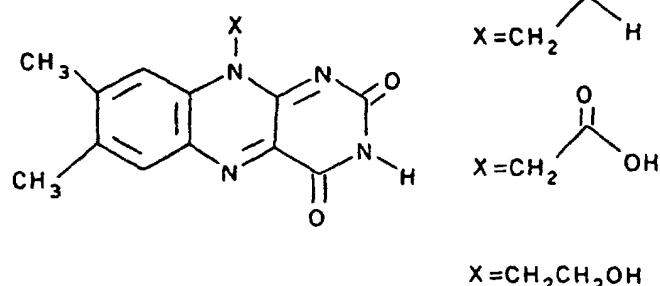


25



- 35 Incomplete photolysis of riboflavin leads to isoalloxazine-containing intermediates (Smith, E.C. and Metzler, D.E. (1963) J. Am. Chem. Soc. **85**:3285-3288; Carins, W.L. and Metzler, D.E. (1971) J. Am. Chem. Soc. **93**:2772-2777; Treadwell, G.E. et al. (1968) J. Chromatog. **35**:376-388). Some of the identified compounds are:

40



50

55

5

10

15

20

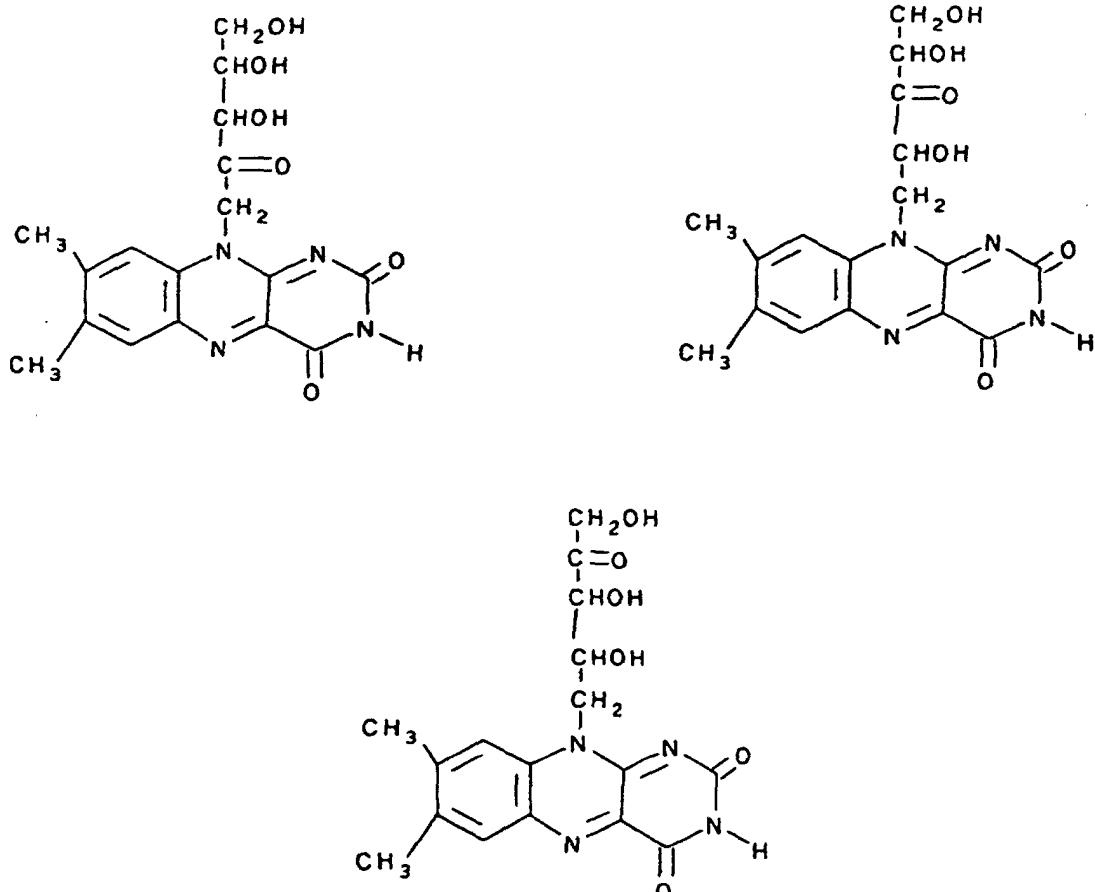
25

30

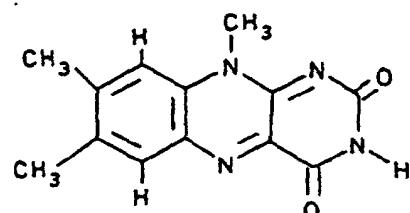
40

45

50



These compounds absorb visible light and may convert to either lumichrome or another riboflavin metabolite, lumiflavin (7,8,10-trimethylisoalloxazine) upon complete photolysis, depending on the experimental conditions.



7,8,10-trimethylisoalloxazine

50

[0009] Lumichrome and lumiflavin are reported to be produced by the photolysis of milk (Parks, O.W. and Allen, C. (1977) *Dairy Sci.* **60**:1038-1041; Toyosaki, T. and Hayashi, A. (1993) *Milewissenschaft* **48**:607-609).

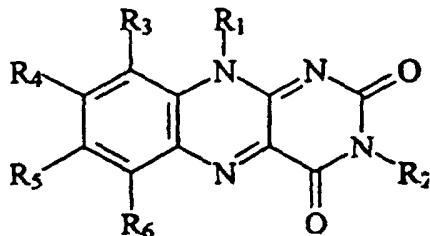
[0010] As a result of the degradation of 7,8-dimethyl-10-ribityl isoalloxazine upon exposure to light, a combination of visible and ultraviolet light is preferred in decontamination procedures using 7,8-dimethyl-10-ribityl isoalloxazine. Since UV light has a higher energy per photon than visible light, and because UV light is absorbed more strongly than visible light by useful compounds in the biological fluid, more damage to the useful components in the biological fluid containing the contaminants will occur when ultraviolet light is used in combination with visible light than when visible light can be used alone.

[0011] There is a need for compounds that neutralize microorganisms with visible light alone.

BRIEF SUMMARY OF THE INVENTION

[0012] Methods are provided for treating a fluid or other material in vitro to totally or partially prevent at least some of the microorganisms and white cells which may be present therein or thereon from replicating. Such fluids may also contain one or more components selected from the group consisting of protein, e.g. biologically active protein such as a therapeutic protein, blood and blood constituents, without destroying the biological activity of such components. The methods comprise:

- (a) adding to said fluid at least 1 μ M of a microorganism neutralizer of formula:



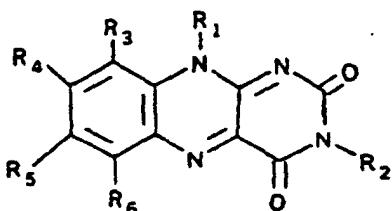
wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, alcohol, amine, polyamine, sulfate, phosphate, halogen selected from the group consisting of chlorine, bromine and iodine, salts of the foregoing, and -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20; wherein an optionally substituted hydrocarbyl group is a group selected from alkyl alkenyl, alkynyl, ether, polyether, thioether, straight chain or cyclic saccharides, ascorbate, aminoalkyl, hydroxyalkyl, thioalkyl, aryl and heterocyclic aryl groups, isoalloxazine molecules, amino acid, polyalcohol, glycol, carbocyclic rings and combinations of such groups, each of which is optionally substituted with halogen(s) OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, where R_a and R_b independently are alkyl, unsaturated alkyl or aryl groups; provided that R1 is not -OH or a straight chain alkyl group where the second carbon of the chain is substituted with -OH or =O and R1, R4 and R5 are not all methyl groups when R2, R3 and R6 are all hydrogen;

(b) exposing the fluid of step (a) to a triggering event of photoradiation or a pH sufficient to activate the microorganism neutralizer, whereby said microorganisms are totally or partially prevented from replicating.

[0013] In one group of compounds, n is an integer between 0 and 5. In another group of compounds, n is an integer from 0 to 10. In another group of compounds, n is an integer from 0 to 20.

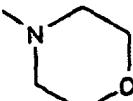
[0014] A fluid is provided comprising biologically active protein, blood or blood constituents, and microorganism neutralizer, obtainable by the method above. The fluid may also contain neutralized microorganisms. A blood product is also provided comprising a microorganism neutralizer obtainable by the method above.

[0015] Compounds are provided having the structure:



wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, alcohol, amine, polyamine, sulfate, phosphate, halogen selected from the group consisting of chlorine, bromine and iodine, salts of the foregoing, and -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other,

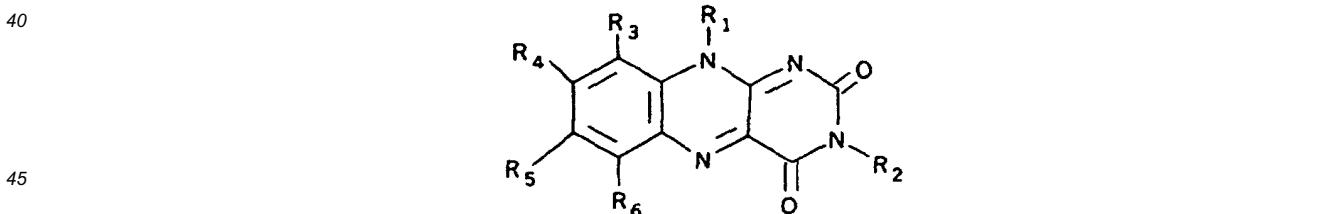
selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20; provided that R1 is not -OH or a straight chain alkyl group where the second carbon of the chain is substituted with -OH or =O; and R1 is not a 2-, 3-, 4- or 5-carbon straight chain alkyl that terminates in -OH, -COH, or -H when R2, R3 and R6 are H, and R4 and R5 are CH₃; R1 is not -CH₂CH₂-(CHOH)₂-CH₃ or -CH₂CH₂-(CHOH)₂-CH₂SO₄ or 1'-D-sorbityl or 1'-D-dulcitol or 1'-D-rhamnityl or 1'-D,L-glyceryl or -CH₂-O-C(O)-CH₃ or -CH₂-O-C(O)-CH₂CH₃ or 2', 3', 4', 5'-di-O-isopropylidene-riboflavin or 8-aminoctyl when R2, R3 and R6 are H and R4 and R5 are CH₃; R1 is not 1'-D-sorbityl or 1'-D-dulcitol when R4 and R5 are both chlorines and when R2, R3 and R6 are all hydrogens; R5 is not ethyl or chloro when R1 and R4 are methyl and R2, R3 and R6 are all hydrogens; R4 and R5 are not both methoxy or both tetramethylene when R1 is methyl and R2, R3 and R6 are all hydrogens; R2 is not -CH₂CH₂NH when R1, R4 and R5 are CH₃ and R3 and R6 are H; R2 is not

15 

when R1, R4 and R5 are CH₃ and R3 and R6 are H; R5 is not chloro when R4 is methoxy and R1 is ethyl-2'N-pyrrolidino and R2, R3, and R6 are hydrogen; R1 is not N,N-dimethylaminopropyl or N,N-diethylaminoethyl when R5 is chloro or methyl and R2, R3, R4 and R6 are hydrogen; R3 is not -NH(CH₂CH₂)Cl when R6 is -NH₂ and R1, R2, R4 and R5 are H; R1, R4 and R5 are not all methyl groups when all of R2, R3 and R6 are hydrogens; R1, R4, R5 and R2 are not all methyl groups when R3 and R6 are hydrogens; R2 is not carboxymethyl when R1, R4 and R5 are methyl and R3 and R6 are hydrogen; R4 is not -NH₂ when R1 and R5 are methyl and R2, R3 and R6 are all hydrogen, R1 is not a phenyl group when R4 and R5 are methyl and R2, R3 and R6 are all H; R1 is not methyl or N,N-dimethylaminoethyl when all of R2, R3, R4, R5 and R6 are hydrogen; R2, R4 and R5 are not all methyl when R1 is acetoxyethyl and R3 and R6 are hydrogen; R5 is not methyl when R1 is N,N-diethylaminoethyl and R2, R3, R4 and R6 are all hydrogen; R4 and R5 are not both chlorine when R1 is methyl and R2, R3 and R6 are all hydrogen; R1 is not ethyl, β-chloroethyl, n-butyl, anilino, benzyl, phenyl, p-tolyl or p-anisyl when R5 is NH₂ and R2, R3, R4 and R6 are all hydrogen; and R4 is not chlorine when R1 is N,N-dimethylaminopropyl and R2, R3, R5 and R6 are all hydrogen.

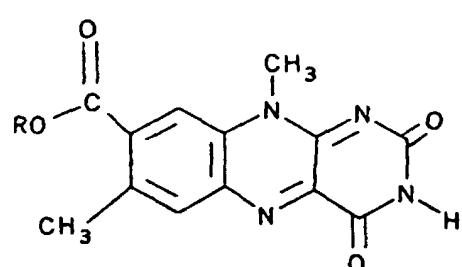
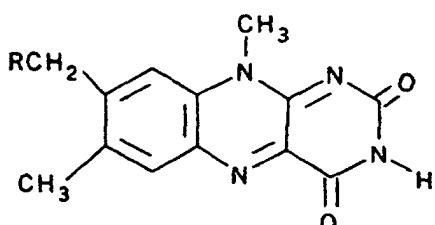
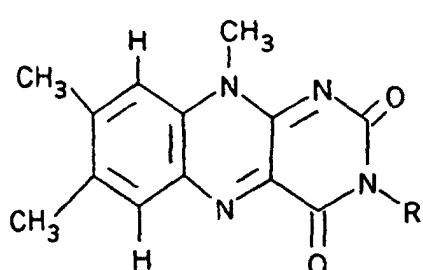
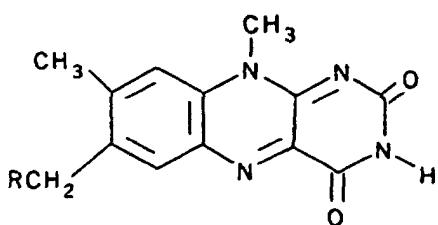
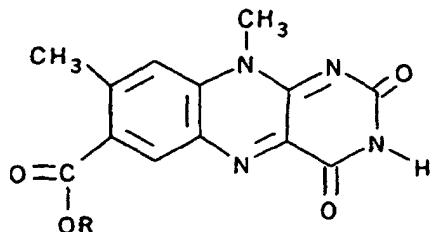
30 [0016] In one group of compounds, n is an integer between 0 and 5. In another group of compounds, n is an integer from 0 to 10. In another group of compounds, n is an integer from 0 to 20.

[0017] Compounds containing any combination of substituents or members of the Markush groups specified above are within the scope of the invention. All compounds of the invention have the ability to neutralize microorganisms. All substituents of the compounds of the invention may be the same, all substituents may be different, or any combination of substituents may be the same or different. Substituents with a specified function, for example those that impart water solubility to the compound, may be included at any of R1-R6. Compounds of the invention include all those compounds with the isoalloxazine backbone (shown below):



45 where R1-R6 are substituted with various substituents, as described elsewhere, except those previously known to the art. The substituents included in the compounds and used in the methods of the invention may be any substituent not having structures or reactivity which would substantially interfere with the desired microorganism neutralization of the microorganism neutralizer, as may readily be determined without undue experimentation by those skilled in the art.

50 [0018] The invention provides a class of compounds wherein a plurality of R1, R2, R3, R4, R5 and R6 are neither CH₃ nor H; and a class of compounds wherein one of R1, R2, R3, R4, R5 and R6 is neither CH₃ nor H. Particular embodiments of compounds of those classes include those wherein a R1, R2, R3, R4, R5 or R6 which is neither CH₃ nor H imparts substantial water solubility to the microorganism neutralizer. Preferred examples of these compounds are:

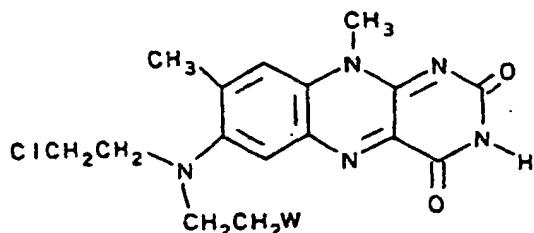


40
wherein R is a substituent imparting water solubility to the molecule, including, but not limited to, ascorbate, alcohol, polyalcohol; amine or polyamines, straight chain or cyclic saccharides, sulfates, phosphates, alkyl chains optionally substituted with -OH at any position, glycols, including polyethylene glycol and polyethers.

45
[0019] Another class of compounds of the invention include those wherein a R1, R2, R3, R4, R5 or R6 that is neither H nor CH₃ contains a halogen or is a halogen, wherein the halogen is selected from the group consisting of fluorine, chlorine, bromine and iodine. Particular embodiments of compounds of this class include compounds where a R1, R2, R3, R4, R5 or R6 that is neither H nor CH₃ is: -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, or is a water soluble group, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen and optionally substituted hydrocarbyl, and n is an integer from 0 to 20.

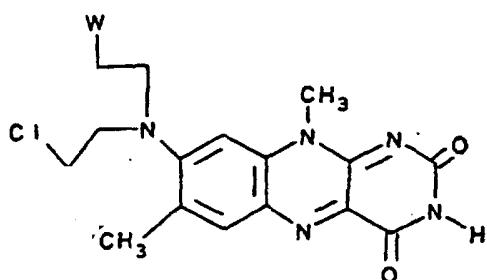
50 [0020] Preferred examples of compounds of this class are:

5



10

15

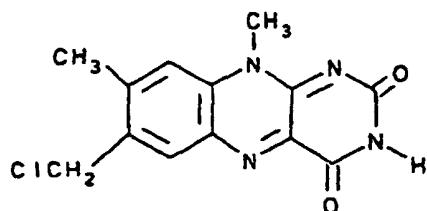


20

where W is a substituent which makes the compound soluble in water at a concentration of at least 10 μM including, but not limited to, ascorbate, alcohol, polyalcohol; amine or polyamines, straight chain or cyclic saccharides, sulfates, phosphates, alkyl chains optionally substituted with -OH at any position, glycols, including polyethylene glycol and polyethers.

[0021] Another particular embodiment of compounds wherein a R1, R2, R3, R4, R5 or R6 that is neither H nor CH₃ contains a halogen or is a halogen includes compounds wherein a R1, R2, R3, R4, R5 or R6 that is neither H nor CH₃ is: X-(CH₂)_n-, wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 6 preferably n is either 1 or 2. A preferred example of compounds of this class include:

35



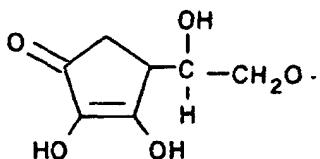
40

[0022] Other classes of compounds of this invention include those wherein R1 is CH₂-(CH₂OH)₃-CH₂OH and those wherein R1 is not CH₂-(CH₂OH)₃-CH₂OH. Also, those compounds wherein R3 and R6 are H are included in the invention.

DEFINITIONS

[0023] A "carbonyl compound" is any compound containing a carbonyl group (-C=O). The term "amine" refers to a primary, secondary, or tertiary amine group. A "polyamine" is a group that contains more than one amine group. A "sulfate" group is a salt of sulfuric acid. Sulfate groups include the group (SO₄)²⁻. "Phosphates" contain the group PO₄³⁻. "Glycols" are groups that have two alcohol groups per molecule of the compound. "Glycols" are also known as diols. A glycol is described by the formula: C_nH_{2n}(OH)₂, where n is an integer. An "aldehyde" is a group containing the formula -(C=O)-H. A "ketone" is a group with formula R-(C=O)-R, where R is not hydrogen. The R groups on ketones do not need to be the same. A "carboxylic acid" is a group which includes the formula: -COOH. An "ether" is a group containing -O-. A "salt" is a group where a hydrogen atom of an acid has been replaced with a metal atom or a positive radical, such as NH₄⁺. "Ascorbate" includes groups with formula:

5



[0024] The term "hydrocarbyl" is used herein to refer generally to organic groups comprised of carbon chains to which hydrogen and optionally other elements are attached. CH₂ or CH groups and C atoms of the carbon chains of the hydrocarbyl may be replaced with one or more heteroatoms (i.e., non-carbon atoms). Suitable heteroatoms include but are not limited to O, S, P and N atoms. The term hydrocarbyl includes, but is not limited to alkyl, alkenyl, alkynyl, ether, polyether, thioether, straight chain or cyclic saccharides, ascorbate, aminoalkyl, hydroxylalkyl, thioalkyl, aryl and heterocyclic aryl groups, optionally substituted isoalloxazine molecules, amino acid, polyalcohol, glycol, groups which have a mixture of saturated and unsaturated bonds, carbocyclic rings and combinations of such groups. The term also includes straight-chain, branched-chain and cyclic structures or combinations thereof. Hydrocarbyl groups are optionally substituted. Hydrocarbyl substitution includes substitution at one or more carbons in the group by moieties containing heteroatoms. Suitable substituents for hydrocarbyl groups include but are not limited to halogens, including chlorine, fluorine, bromine and iodine, OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, where R_a and R_b independently are alkyl, unsaturated alkyl or aryl groups.

[0025] The term "alkyl" takes its usual meaning in the art and is intended to include straight-chain, branched and cycloalkyl groups. The term includes, but is not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,1-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2-ethylbutyl, 1-ethylbutyl, 1,3-dimethylbutyl, n-heptyl, 5-methylhexyl, 4-methylhexyl, 3-methylhexyl, 2-methylhexyl, 1-methylhexyl, 3-ethylpentyl, 2-ethylpentyl, 1-ethylpentyl, 4,4-dimethylpentyl, 3,3-dimethylpentyl, 2,2-dimethylpentyl, 1,1-dimethylpentyl, n-octyl, 6-methylheptyl, 5-methylheptyl, 4-methylheptyl, 3-methylheptyl, 2-methylheptyl, 1-methylheptyl, 1-ethylhexyl, 1-propylpentyl, 3-ethylhexyl, 5,5-dimethylhexyl, 4,4-dimethylhexyl, 2,2-diethylbutyl, 3,3-diethylbutyl, and 1-methyl-1-propylbutyl. Alkyl groups are optionally substituted. Lower alkyl groups are C₁-C₆ alkyl and include among others methyl, ethyl, n-propyl, and isopropyl groups.

[0026] The term "cycloalkyl" refers to alkyl groups having a hydrocarbon ring, particularly to those having rings of 3 to 7 carbon atoms. Cycloalkyl groups include those with alkyl group substitution on the ring. Cycloalkyl groups can include straight-chain and branched-chain portions. Cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl. Cycloalkyl groups can optionally be substituted.

[0027] Aryl groups may be substituted with one, two or more simple substituents including, but not limited to, lower alkyl, e.g., methyl, ethyl, butyl; halo, e.g., chloro, bromo; nitro; sulfato; sulfonyloxy; carboxy; carbo-lower-alkoxy, e.g., carbomethoxy, carbethoxy; amino; mono- and di-lower-alkylamino, e.g., methylamino, ethylamino, dimethylamino, methylethylamino; amido; hydroxy; lower-alkoxy, e.g., methoxy, ethoxy; and lower-alkanoyloxy, e.g., acetoxy.

[0028] The term "unsaturated alkyl" group is used herein generally to include alkyl groups in which one or more carbon-carbon single bonds have been converted to carbon-carbon double or triple bonds. The term includes alkenyl and alkynyl groups in their most general sense. The term is intended to include groups having more than one double or triple bond, or combinations of double and triple bonds. Unsaturated alkyl groups include, without limitation, unsaturated straight-chain, branched or cycloalkyl groups. Unsaturated alkyl groups include without limitation: vinyl, allyl, propenyl, isopropenyl, butenyl, pentenyl, hexenyl, hexadienyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, 1-propenyl, 2-butenyl, 2-methyl-2-but enyl, ethynyl, propargyl, 3-methyl-1-pentynyl, and 2-heptynyl. Unsaturated alkyl groups can optionally be substituted.

[0029] Substitution of alkyl, cycloalkyl and unsaturated alkyl groups includes substitution at one or more carbons in the group by moieties containing heteroatoms. Suitable substituents for these groups include but are not limited to OH, SH, NH₂, COH, CO₂H, OR_c, SR_c, P, PO, NR_cR_d, CONR_cR_d, and halogens, particularly chlorines and bromines where R_c and R_d, independently, are alkyl, unsaturated alkyl or aryl groups. Preferred alkyl and unsaturated alkyl groups are the lower alkyl, alkenyl or alkynyl groups having from 1 to about 3 carbon atoms.

[0030] The term "aryl" is used herein generally to refer to aromatic groups which have at least one ring having a conjugated pi electron system and includes without limitation carbocyclic aryl, aralkyl, heterocyclic aryl, biaryl groups and heterocyclic biaryl, all of which can be optionally substituted. Preferred aryl groups have one or two aromatic rings.

[0031] "Carbocyclic aryl" refers to aryl groups in which the aromatic ring atoms are all carbons and includes without limitation phenyl, biphenyl and naphthalene groups.

[0032] "Aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include among others

benzyl, phenethyl and picolyl, and may be optionally substituted. Aralkyl groups include those with heterocyclic and carbocyclic aromatic moieties.

[0033] "Heterocyclic aryl groups" refers to groups having at least one heterocyclic aromatic ring with from 1 to 3 heteroatoms in the ring, the remainder being carbon atoms. Suitable heteroatoms include without limitation oxygen, sulfur, and nitrogen. Heterocyclic aryl groups include among others furanyl, thienyl, pyridyl, pyrrolyl, N-alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl, benzofuranyl, quinolinyl, and indolyl, all optionally substituted.

[0034] "Heterocyclic biaryl" refers to heterocyclic aryls in which a phenyl group is substituted by a heterocyclic aryl group ortho, meta or para to the point of attachment of the phenyl ring to the decalin or cyclohexane. Heterocyclic biaryl includes among others groups which have a phenyl group substituted with a heterocyclic aromatic ring. The aromatic rings in the heterocyclic biaryl group can be optionally substituted.

[0035] "Biaryl" refers to carbocyclic aryl groups in which a phenyl group is substituted by a carbocyclic aryl group ortho, meta or para to the point of attachment of the phenyl ring to the decalin or cyclohexane. Biaryl groups include among others a first phenyl group substituted with a second phenyl ring ortho, meta or para to the point of attachment of the first phenyl ring to the decalin or cyclohexane structure. Para substitution is preferred. The aromatic rings in the biaryl group can be optionally substituted.

[0036] Aryl group substitution includes substitutions by non-aryl groups (excluding H) at one or more carbons or where possible at one or more heteroatoms in aromatic rings in the aryl group. Unsubstituted aryl, in contrast, refers to aryl groups in which the aromatic ring carbons are all substituted with H, e.g. unsubstituted phenyl (-C₆H₅), or naphthyl (-C₁₀H₇). Suitable substituents for aryl groups include among others, alkyl groups, unsaturated alkyl groups, halogens, OH, SH, NH₂, COH, CO₂H, OR_e, SR_e, NR_eR_f, CONR_eR_f, where R_e and R_f independently are alkyl, unsaturated alkyl or aryl groups. Preferred substituents are OH, SH, OR_e, and SR_e where R_e is a lower alkyl, i.e., an alkyl group having from 1 to about 3 carbon atoms. Other preferred substituents are halogens, more preferably chlorine or bromine, and lower alkyl and unsaturated lower alkyl groups having from 1 to about 3 carbon atoms. Substituents include bridging groups between aromatic rings in the aryl group, such as -CO₂-, -CO-, -O-, -S-, -P-, -NH-, -CH=CH- and -(CH₂)_ℓ where ℓ is an integer from 1 to about 5, and particularly -CH₂-.

Examples of aryl groups having bridging substituents include phenylbenzoate. Substituents also include moieties, such as -(CH₂)_ℓ, -O-(CH₂)_ℓ or -OCO-(CH₂)_ℓ, where ℓ is an integer from about 2 to 7, as appropriate for the moiety, which bridge two ring atoms in a single aromatic ring as, for example, in a 1, 2, 3, 4-tetrahydronaphthalene group. Alkyl and unsaturated alkyl substituents of aryl groups can in turn optionally be substituted as described *supra* for substituted alkyl and unsaturated alkyl groups.

[0037] The terms "alkoxy group" and "thioalkoxy group" (also known as mercaptide groups, the sulfur analog of alkoxy groups) take their generally accepted meaning. Alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, n-pentyloxy, neopentyloxy, 2-methylbutoxy, 1-methylbutoxy, 1-ethyl propoxy, 1,1 -dimethylpropoxy, n-hexyloxy, 1-methylpentylxyloxy, 2-methylpentylxyloxy, 3-methylpentylxyloxy, 4-methylpentylxyloxy, 3,3-dimethylbutoxy, 2,2-dimethoxybutoxy, 1-1-dimethylbutoxy, 2-ethylbutoxy, 1-ethylbutoxy, 1,3-dimethylbutoxy, n-pentyloxy, 5-methylhexyloxy, 4-methylhexyloxy, 3-methylhexyloxy, 2-methylhexyloxy, 1-methylhexyloxy, 3-ethylpentylxyloxy, 2-ethylpentylxyloxy, 1-ethylpentylxyloxy, 4,4-dimethylpentylxyloxy, 3,3-dimethylpentylxyloxy, 2,2-dimethylpentylxyloxy, 1,1-dimethylpentylxyloxy, n-octyloxy, 6-methylheptyloxy, 5-methylheptyloxy, 4-methylheptyloxy, 3-methylheptyloxy, 2-methylheptyloxy, 1-methylheptyloxy, 1-ethylhexyloxy, 1-propylpentylxyloxy, 3-ethylhexyloxy, 5,5-dimethylhexyloxy, 4,4-dimethylhexyloxy, 2,2-diethylbutoxy, 3,3-diethylbutoxy, 1-methyl-1-propylbutoxy, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, sec-butoxymethyl, isobutoxymethyl, (1-ethyl propoxy)methyl, (2-ethylbutoxy)methyl, (1-ethylbutoxy)methyl, (2-ethylpentylxyloxy)methyl, (3-ethylpentylxyloxy)methyl, 2-methoxyethyl, 1-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 2-methoxypropyl, 1-methoxypropyl, 2-ethoxypropyl, 3-(n-propoxy)propyl, 4-methoxybutyl, 2-methoxybutyl, 4-ethoxybutyl, 2-ethoxybutyl, 5-ethoxypentyl, and 6-ethoxyhexyl. Thioalkoxy groups include but are not limited to the sulfur analogs of the alkoxy groups specifically listed *supra*.

[0038] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted phenyl" means that the phenyl radical may or may not be substituted and that the description includes both unsubstituted phenyl radicals and phenyl radicals wherein there is substitution.

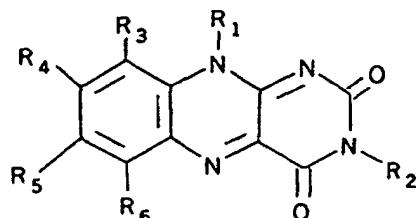
[0039] "Amino acids" as used herein include naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, ornithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, o-, m-, and p-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. "Amino acid" as used herein includes amino acid residues and amino acid side chains. An "amino acid residue" is an amino acid radical -NHCH(R)C(O)-, wherein R is an amino acid side chain, except for the amino acid residues of proline and hydroxyproline which are --N(CH₂-CH₂-CH₂)CHC(O)-- and --N(CH-CHOHCH₂)CHC(O)--, respectively. An amino acid side chain is a radical found on the α-carbon of an α-amino acid as defined herein, where the radical is either hydrogen (side chain of glycine), methyl (side chain of alanine), or is a radical bonded to the α-carbon by a methylene (--CH₂--), or phenyl group.

[0040] A protected glucose derivative takes its usual meaning in the art and includes a glucose molecule wherein some of the hydroxyl groups are substituted with acetate groups.

[0041] "Contacting" reaction components with each other refers to providing a medium and/or reaction chamber in which the reaction components are placed together so that they can react with each other. Preferably, the reaction components are suspended or dissolved in a carrier fluid which is a liquid medium. "Maintaining reaction components in contact" means keeping the components together in such a way that they can react with each other.

[0042] "Straight chain or cyclic saccharides" include mono-, di- and poly-, straight chain and cyclic saccharides that are optionally substituted with an amino group which is optionally acetylated. Straight chain saccharides that are useful in this invention include but are not limited to those molecules with a chain of 5 or 6 carbon atoms with one or more -OH groups attached, and either an aldehyde or ketone group. Cyclic saccharides are saccharides that are in a ring form. Disaccharides are compounds wherein two monosaccharide groups are linked. Polysaccharides are compounds wherein more than two monosaccharide groups are linked. Specific examples of saccharides useful in this invention include glucose, ribose and glucosamine, among others.

[0043] "Isoalloxazine", "isoalloxazine derivative" or "core structure of isoalloxazine" include compounds that comprise the structure:



where R1-R6 are substituted with various substituents, as described elsewhere.

[0044] As used herein, the term "neutralization of a microorganism" or "neutralizing" means totally or partially preventing the microorganism from replicating, either by killing the microorganism or otherwise interfering with its ability to reproduce. A "neutralizer" is a compound that is capable of neutralizing a microorganism. The neutralizers useful in this invention include molecules with the core structure of isoalloxazine, as defined above. To "activate the microorganism neutralizer" is to expose the microorganism neutralizer to a triggering event that causes it to become active toward neutralizing microorganisms.

[0045] Microorganisms include viruses (both extracellular and intracellular), bacteria, bacteriophages, fungi, blood-transmitted parasites, and protozoa. Exemplary viruses include acquired immunodeficiency (HIV) virus, hepatitis A, B and C viruses, sinbis virus, cytomegalovirus, vesicular stomatitis virus, herpes simplex viruses, e.g. types I and II, human T-lymphotropic retroviruses, HTLV-III, lymphadenopathy virus LAV/IDAV, parvovirus, transfusion-transmitted (TT) virus, Epstein-Barr virus, and others known to the art. Bacteriophages include Φ X174, Φ 6, λ , R17, T₄, and T₂. Exemplary bacteria include *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *L. monocytogenes*, *E. coli*, *K. pneumonia* and *S. marcescens*. Neutralization of white blood cells may be desirable when suppression of immune or autoimmune response is desired, e.g., in processes involving transfusion of red cells, platelets or plasma when donor white blood cells may be present.

[0046] "Triggering event" refers to the stimulus that activates the microorganism neutralizer. Triggering events are exposure of the neutralizer to an neutralization effective wavelength of light, or a pH sufficient to activate the neutralizer to neutralize microorganisms.

[0047] "Water soluble group" includes a group that, when included as a substituent on the neutralizer, imparts substantial solubility in water to the compound. Typically, the compound is soluble in water at a concentration of about 10 - 150 μ M. Water soluble groups as referred to in this invention include, but are not limited to alcohols; polyalcohols; straight chain or cyclic saccharides; amines and polyamines; sulfate groups; phosphate groups; ascorbate groups; alkyl chains optionally substituted with -OH at any position; glycols, including polyethylene glycols, and polyethers.

[0048] The term "biologically active" means capable of effecting a change in a living organism or component thereof. "Biologically active" with respect to "biologically active protein" as referred to herein does not refer to proteins which are part of the microorganisms being neutralized. Similarly, "non-toxic" with respect to the neutralizers means low or no toxicity to humans and other mammals, and does not mean non-toxic to the microorganisms being neutralized. "Substantial destruction" of biological activity means at least as much destruction as is caused by porphyrin and porphyrin derivatives, metabolites and precursors which are known to have a damaging effect on biologically active proteins and cells of humans and mammals. Similarly, "substantially non-toxic" means less toxic than porphyrin, porphyrin derivatives, metabolites and precursors that are known for blood sterilization. Preferably, neutralizers are less toxic

than porphyrin, porphyrin derivatives, metabolites and precursors that are known for blood sterilization.

[0049] The term "blood product" as used herein includes blood constituents and therapeutic protein compositions containing proteins derived from blood as defined above. Fluids containing biologically active proteins other than those derived from blood may also be treated by the methods of this invention. Such fluids may also contain one or more components selected from the group consisting of protein, e.g. biologically active protein such as a therapeutic protein, blood and blood constituents, without destroying the biological activity of such components.

[0050] Decontamination methods of this invention using isoalloxazine derivatives as defined above do not substantially destroy the biological activity of fluid components other than microorganisms. As much biological activity of these components as possible is retained, although in certain instances, when the methods are optimized, some loss of biological activity, e.g., denaturation of protein components, must be balanced against effective decontamination of the fluid. So long as fluid components retain sufficient biological activity to be useful for their intended or natural purposes, their biological activities are not considered to be substantially destroyed.

[0051] "Decomposition" of the neutralizer upon exposure to light refers to the chemical transformation of the neutralizer into new compounds. An example of decomposition of the neutralizer is the production of lumichrome upon exposure of riboflavin to visible light.

[0052] A "photosensitizer" is defined as any compound which absorbs radiation of one or more defined wavelengths and subsequently utilizes the absorbed energy to carry out a chemical process. Photosensitizers of this invention may include compounds which preferentially adsorb to nucleic acids, thus focusing their photodynamic effect upon microorganisms and viruses with little or no effect upon accompanying cells or proteins. Other photosensitizers of this invention are also useful, such as those using singlet oxygen-dependent mechanisms.

[0053] An "alkylating agent" is a compound that reacts with amino acid residues and nucleic bases and inhibits replication of microorganisms.

DETAILED DESCRIPTION OF THE INVENTION

[0054] The contaminant neutralizers of the invention neutralize microorganisms by exposure to a triggering event of either exposure to an activation-effective wavelength of light in the uv/visible region of the spectrum or an activation-effective pH. The neutralizer must be one which does not substantially destroy desired components of the fluid being decontaminated, and also preferably which does not degrade into products which substantially destroy desired components or have significant toxicity or substantially decompose into ultraviolet light absorbing compounds.

[0055] In embodiments of the invention using light as a triggering event, the fluid containing an appropriate concentration of the neutralizer is exposed to photoradiation of the appropriate wavelength to activate the neutralizer, using an amount of photoradiation sufficient to activate the neutralizer, but less than that which would cause substantial damage to the biological components or substantially interfere with biological activity of other proteins present in the fluid. The wavelength of light used and the amount of radiation used will depend on the neutralizer selected, as is known to the art or readily determinable without undue experimentation by one of ordinary skill in the art, using literature sources or direct measurement. Preferably the light source is a uv/visible light source providing 320 nm to about 700 nm, and more preferably about 365 nm to about 650 nm of radiation. The amount of neutralizer to be mixed with the fluid will be an amount sufficient to adequately neutralize microorganisms therein. Preferably the neutralizer is soluble in the fluid and present in an amount less than the upper solubility limit of the neutralizer in the fluid. As taught herein, optimal concentrations for desired neutralizers may be readily determined by those skilled in the art without undue experimentation. Preferably, the smallest efficacious concentration of neutralizer is used. The neutralizer is used in a concentration of at least 1 μ M up to the solubility of the neutralizer in the fluid, and typically the concentration of neutralizer is about 10 μ M. Other concentrations are also able to be used. An excess of neutralizer may be present in the solution. The neutralizer may also be used in a suspension, where the neutralizer is not soluble in the fluid, provided that adequate mixing is provided to contact the neutralizer with the fluid. The neutralizer may also be removed from the fluid prior to administration of the fluid to a patient. All other parameters that may be involved in a decontamination system, including appropriate temperatures for the reaction of the neutralizer as well as the ranges of temperature, photoradiation intensity and duration, and neutralizer concentration which will optimize microbial neutralization and minimize damage to desired proteins and/or cellular components in the fluid are also easily determined as is known in the art or readily determinable without undue experimentation by one of ordinary skill in the art, using literature sources or direct measurement.

[0056] In embodiments of this invention using pH to neutralize the contaminants, the appropriate pH, concentration of neutralizer that is effective, and other parameters are determined by means known to one of ordinary skill in the art.

In particular embodiments, contacting the contaminant neutralizer with the fluid containing microorganisms to be neutralized may be sufficient to activate the contaminant neutralizer (i.e., the triggering event when pH is used to activate the microorganism neutralizer may not need to be externally applied). An effective concentration is generally from about 10 - 100 μ M. A pH of about 5 to about 8 is generally effective to activate the neutralizer. Other concentrations

and pH's may be used.

[0057] A solution or suspension of contaminant neutralizer may be prepared and stored and when desired, used by contacting with fluid or other substance containing contaminants and exposing to a triggering event.

[0058] Once such system requirements have been determined, the appropriate apparatus may be designed. Batch or flow-through systems may be used, for example. The isoalloxazine derivatives of this invention can be used in the decontamination systems described in U.S. Patent Nos. 5,290,221, 5,536,238, 5,290,221 and 5,536,238, and U.S. Patent Application Nos. 09/119,666 and 09/357,188. In general, the fluid to be decontaminated is mixed with neutralizer. If light is used to neutralize the contaminants, the fluid and neutralizer are irradiated with a sufficient amount of photoradiation at an appropriate wavelength to activate the neutralizer to react with microorganisms in the fluid such that microorganisms in the fluid are neutralized. If pH is used to neutralize the contaminants, the pH of the fluid and neutralizer is changed, if necessary, by any means known in the art.

[0059] Examples of materials which may be treated by the methods of this invention are whole blood and aqueous compositions containing biologically active proteins derived from blood or blood constituents. Packed red cells, platelets and plasma (fresh or fresh frozen plasma) are exemplary of such blood constituents. In addition, therapeutic protein compositions containing proteins derived from blood, such as fluids containing biologically active protein useful in the treatment of medical disorders, e.g., factor VIII, Von Willebrand factor, factor IX, factor X, factor XI, Hageman factor, prothrombin, anti-thrombin III, fibronectin, plasminogen, plasma protein fraction, immune serum globulin, modified immune globulin, albumin, plasma growth hormone, somatomedin, plasminogen streptokinase complex, ceruloplasmin, transferrin, haptoglobin, antitrypsin and prekallikrein may be treated by the decontamination methods of this invention. Other fluids which could benefit from the treatment of this invention are peritoneal solutions used for peritoneal dialysis which are sometimes contaminated during connection, leading to peritoneal infections.

[0060] This method is also useful for treating other fluids including fluids which are meant for nourishment of humans or animals such as water, fruit, juices, milk, broths, soups and the like. The method is also useful for treating parenteral solutions. This invention may also be used to treat surfaces, as described in United States Patent Application No. 09/119,666. The isoalloxazine derivative compounds of this invention may also coat surfaces such as blood or peritoneal dialysis tubing sets to assure sterile connections and sterile docking.

[0061] The neutralizer may be applied in a suitable carrier such as water or a solution containing other treatment additives, by spraying, dipping, wiping on, or by other means known to the art. The amount of neutralizer and the conditions to activate the neutralizer required for treatment will be readily determined by one of skill in the art without undue experimentation depending on the level of contamination and the material being treated.

[0062] The activated neutralizer is capable of neutralizing the microorganisms present, such as by interfering to prevent their replication. This may occur with activation of the molecule with uv/visible light, or may occur by the nature of the substituent on the isoalloxazine core and an alteration of the pH of the system in the absence of light. Specificity of action of the neutralizer may be conferred by the close proximity of the neutralizer to the nucleic acid of the microorganism and this may result from binding of the neutralizer to the nucleic acid. "Nucleic acid" includes ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Other Neutralizers may act by binding to cell membranes or by other mechanisms. The neutralizer may also be targeted to the microorganism to be neutralized by covalently coupling to an antibody, preferably a specific monoclonal antibody to the microorganism.

[0063] Enhancers may also be added to the fluid to make the process more efficient and selective. Such enhancers include antioxidants or other agents to prevent damage to desired fluid components or to improve the rate of neutralization of microorganisms and are exemplified by adenine, histidine, cysteine, tyrosine, tryptophan, ascorbate, N-acetyl-L-cysteine, propyl gallate, glutathione, mercaptopropionylglycine, dithiothreitol, nicotinamide, BHT, BHA, lysine, serine, methionine, glucose, mannitol, trolox, glycerol, and mixtures thereof.

[0064] The use of the compounds of this invention to neutralize microorganisms requires mixing or contacting the isoalloxazine derivative with the material to be decontaminated. Mixing or contacting may be done by simply adding the neutralizer or a solution containing the neutralizer to a fluid to be decontaminated. In one embodiment using light to neutralize the microorganisms, the material to be decontaminated to which a light-triggered neutralizer has been added is flowed past a photoradiation source, and the flow of the material generally provides sufficient turbulence to distribute the neutralizer throughout the fluid to be decontaminated. In another embodiment, the fluid and light-triggered neutralizer are placed in a photopermeable container and irradiated in batch mode, preferably while agitating the container to fully distribute the photosensitizer and expose all the fluid to the radiation. In another embodiment, insoluble materials may be used in the process of this invention, for example, by suspending the isoalloxazine derivative in the biological fluid and exposing the fluid and isoalloxazine derivative to the triggering event. In another embodiment, the pH-triggered compound is placed in contact with the fluid to be treated. In some embodiments using a pH-triggered compound, the pH of the fluid-compound mixture will require changing in order to trigger neutralization by means known to one of ordinary skill in the art, such as the use of acid or base.

EXAMPLES

Example 1. Absorbance Profile of isoalloxazine derivative

[0065] A sample of an isoalloxazine derivative is analyzed using a scanning UV spectrophotometer over the region 200 to 900 nm. For analysis, the sample is dissolved in distilled water. An absorption spectrum is obtained, and extinction coefficients at the absorbance maxima and other wavelengths of interest are determined. From the absorption spectrum and extinction coefficients, appropriate wavelengths for irradiation are determined. An appropriate wavelength is one at which the extinction coefficient is sufficient to ensure adequate activation of the sensitizer in solution.

Example 2. Neutralization of microorganisms with isoalloxazine derivatives using light

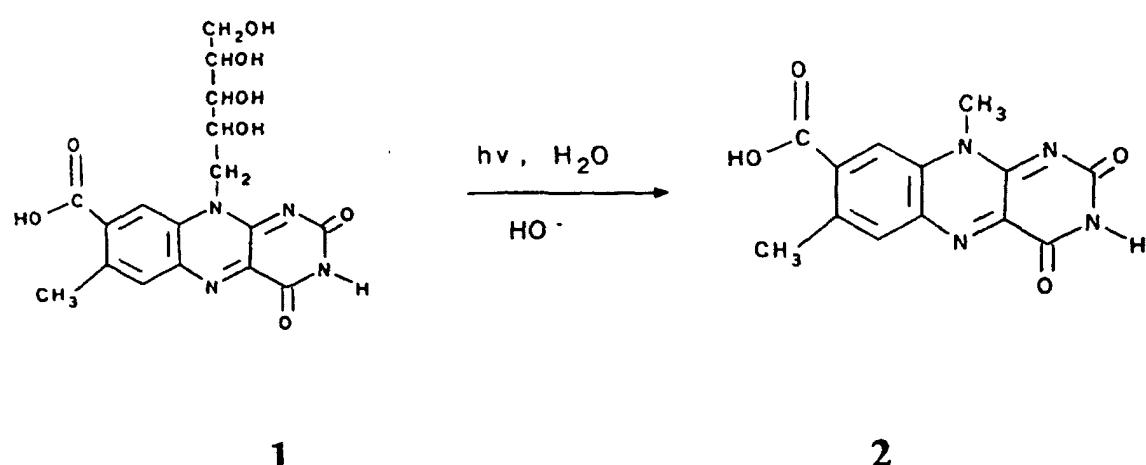
[0066] 7, 8, 10-trimethyl, 3-sulfonyl isoalloxazine is dissolved in blood at a concentration of 10 μM . The sample is spiked with a representative microorganism. Flow of the sample through an irradiation chamber is maintained and the sample is irradiated with a neutralization-effective level of light at a wavelength determined to be appropriate for neutralization, as described above. The extent of neutralization of the microorganism is measured by methods known in the art.

Example 3. pH sensitivity studies

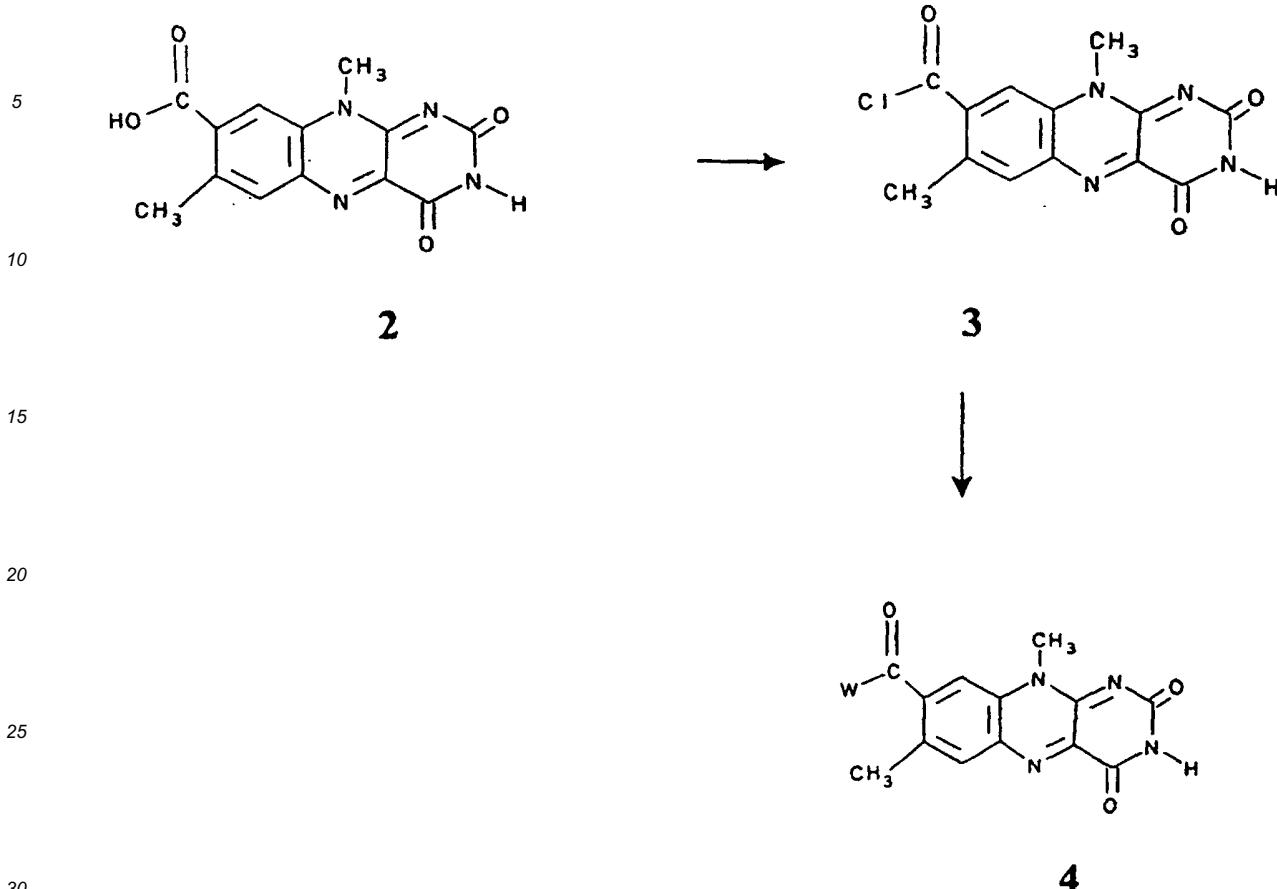
[0067] 7-chloroethylamino-8,10-methyl isoalloxazine is dissolved in blood at concentrations of 10 - 100 μM . The solutions are spiked with a representative microorganism. Aliquots are removed and the pH of different aliquots is adjusted to 1.0, 3.0, 5.0, 7.0, 9.0 with sodium carbonates. The solutions are mixed to distribute the components. The neutralization results are determined as described above.

Synthesis

[0068] Carboxyriboflavin (1, McCormick, D. (1970) J. Heter. Chem. 7:447) is photolyzed in aqueous alkali to form a carboxylumiflavine (2).

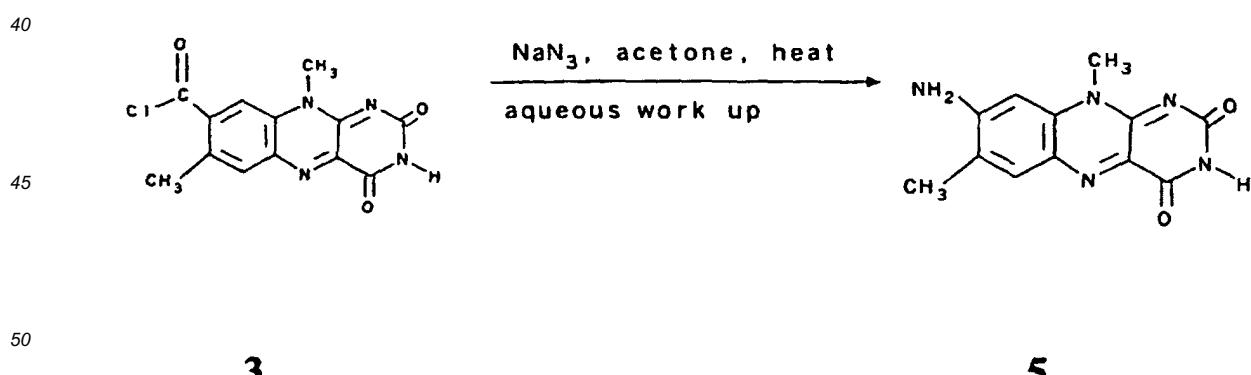


[0069] Compound 2 is converted to an acid chloride 3 with oxallylchloride.



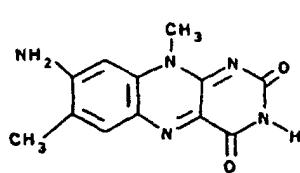
[0070] Compound 3 is reacted with ascorbate ion, glucosamine, a protected glucose derivative or di or triethylene glycol to form a water soluble derivative 4 where the light sensitive water soluble moiety W is far removed from the amide containing ring.

[0071] Compound 3 is reacted with sodium azide in acetone to effect a Curtius Rearrangement. This forms compound 5, upon work-up. This reaction effectively replaces a CO₂H group with an NH₂ group.

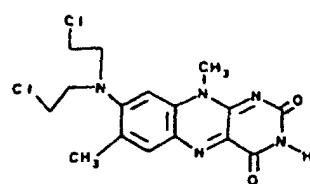
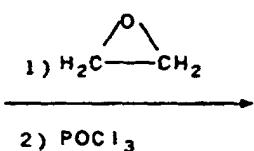


Lumiflavine amine 5 is converted into compound 6 by the procedure of J.L. Everett, et al. (1953) J. Chem. Soc., p 2386.

5



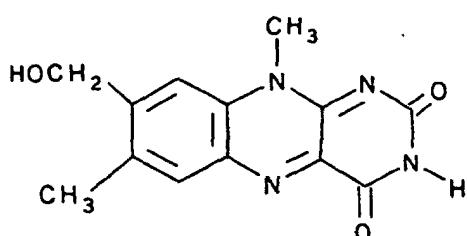
10

5**6**

[0072] One of the chlorines from 6 will be replaced with W to impart water solubility to the compound.

[0073] Riboflavin methanol is synthesized by the method of McCormick and upon photolysis it will yield lumiflavine methanol 7.

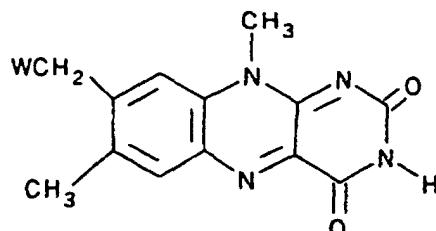
20



25

7

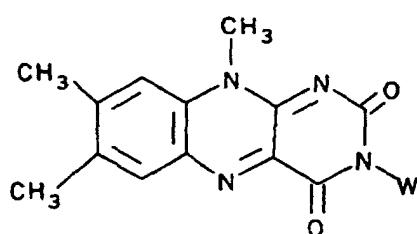
30

**8**

[0074] The hydroxyl group is replaced with a water soluble group (e.g., W, 8) as described earlier.

[0075] The N-3 (R2) of lumiflavine is alkylated using the method of P. Hemmerich (1964) *Helv. Chim. Acta* **47**:464. This method is adapted to place water soluble groups at (R2) (e.g., 9).

35



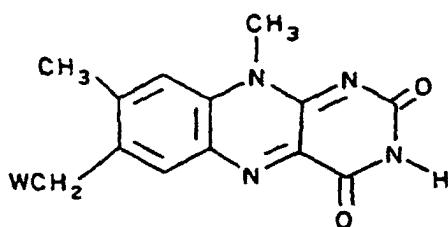
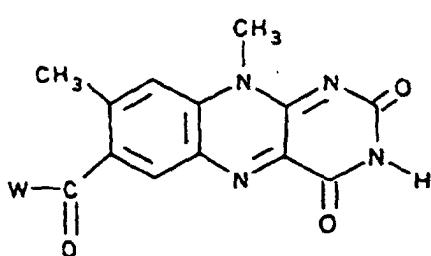
45

9

55

[0076] This lumiflavine will be water soluble, absorb visible light, and should not break down upon photolysis with visible light.

[0077] The corresponding series 10 and 11 are formed by application of known reactions.

**10****11**

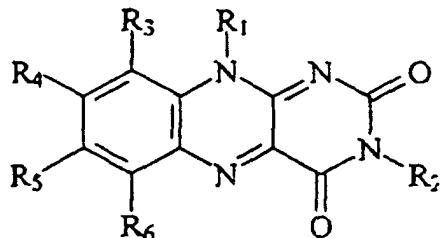
15 [0078] All compounds of this invention may be prepared by the methods above or by methods well known in the art, or by adapting the methods above or methods well known in the art. In addition, reactants specified herein may be substituted for others that produce a similar function.

20

Claims

25 1. A method for treating a fluid in vitro to totally or partially prevent microorganisms which may be present therein from replicating, said method comprising:

(a) adding to said fluid at least 1 μ M of a microorganism neutralizer of formula:



40 wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, alcohol, amine, polyamine, sulfate, phosphate, halogen selected from the group consisting of chlorine, bromine and iodine, salts of the foregoing;

45 and -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20;

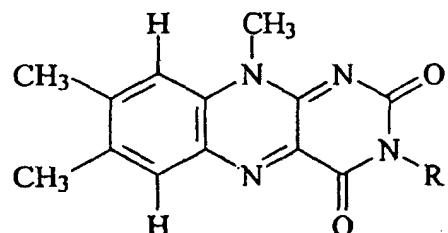
50 wherein an optionally substituted hydrocarbyl group is a group selected from alkyl, alkenyl, alkynyl, ether, polyether, thioether, straight chain or cyclic saccharides, ascorbate, aminoalkyl, hydroxyalkyl, thioalkyl, aryl and heterocyclic aryl groups, isoalloxazine molecules, amino acid, polyalcohol, glycol, carbocyclic rings and combinations of such groups, each of which is optionally substituted with halogen(s) OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, where R_a and R_b independently are alkyl, unsaturated alkyl or aryl groups;

55 provided that R1 is not -OH or a straight chain alkyl group where the second carbon of the chain is substituted with -OH or =O and R1, R4 and R5 are not all methyl groups when R2, R3 and R6 are all hydrogen;

(b) exposing the fluid of step (a) to a triggering event of photoradiation or a pH sufficient to activate the microorganism neutralizer whereby said microorganisms are totally or partially prevented from replicating.

2. The method of claim 1, wherein said fluid is a food product, a drink meant for human or animal consumption or a peritoneal dialysis solution.
- 5 3. A method according to claim 1, wherein said fluid contains one or more components selected from the group consisting of protein, blood, and blood constituents.
- 10 4. The method of claim 3, wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen, optionally substituted alcohol, straight chain or cyclic saccharide, amino acid, amine, polyamine, polyether, polyalcohol, sulfate, phosphate, carbonyl, glycol, halogen selected from the group consisting of chlorine, bromine and iodine, aldehyde, ketone, carboxylic acid and ascorbate.
- 15 5. The method of claim 3, wherein said triggering event is photoradiation sufficient to activate the microorganism neutralizer.
- 16 6. The method of claim 3, wherein said triggering event is a pH sufficient to activate the microorganism neutralizer.
- 20 7. The method of claim 3, wherein said microorganisms are selected from the group consisting of HIV viruses, hepatitis viruses, sindbis virus, cytomegalovirus, vesicular stomatitis virus, herpes simplex viruses, vaccinia virus, human T-lymphotropic retroviruses, HTLV-III, lymphadenopathy virus LAV/IDAV, parvovirus, transfusion-transmitted (TT) virus, Epstein-Barr virus, bacteriophages Φ X174, Φ 6, λ , R17, T_4 , T_2 , *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *L. monocytogenes*, *E. coli*, *K. pneumoniae* and *S. marcescens*.
- 25 8. The method of claim 3, wherein said microorganism neutralizer is selected from

(a)

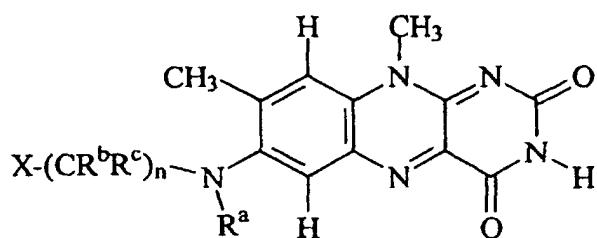


30

35

wherein R is selected from the group consisting of ascorbate, alcohol, polyalcohol, amine, polyamine, straight chain or cyclic saccharides, sulfates, phosphates, polyethylene glycols, and polyethers;

(b)



40

45

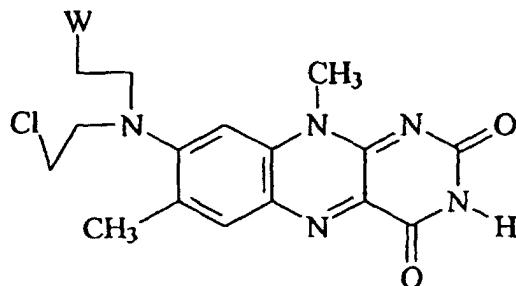
50

wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20; or

55

5

(c)



10

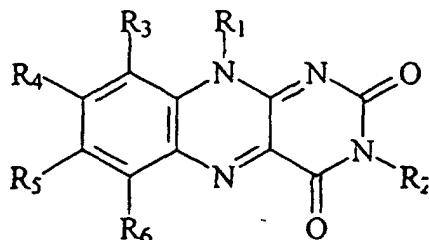
wherein W is a group which makes the neutralizer soluble in water at a concentration of at least 10 μM .

- 15 9. The method of claim 3, wherein said fluid comprises platelets, red blood cells, serum or plasma separated from whole blood.
10. The method of claim 3, wherein said microorganism neutralizer is added to anticoagulant and said anticoagulant is added to said fluid.
- 20 11. The method of claim 3, wherein an antioxidant is added to said fluid prior to exposing said fluid to said triggering event.
- 25 12. The method of claim 3, wherein if said microorganism neutralizer produces photolytic products, the photolytic products are less toxic than porphyrin to humans or animals.
13. A method of totally or partially preventing microorganisms on a surface from replicating, comprising:

30

- (a) applying to said surface at least 1 μM of a compound of formula:

35



40

wherein R₁, R₂, R₃, R₄, R₅ and R₆ are, independently from one another, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, alcohol, amine, polyamine, sulfate, phosphate, halogen selected from the group consisting of chlorine, bromine and iodine, salts of the foregoing;

45 and -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20;

50 wherein an optionally substituted hydrocarbyl group is a group selected from alkyl, alkenyl, alkynyl, ether, polyether, thioether, straight chain or cyclic saccharides, ascorbate, aminoalkyl, hydroxyalkyl, thioalkyl, aryl and heterocyclic aryl groups, isoalloxazine molecules, amino acid, polyalcohol, glycol, carbocyclic rings and combinations of such groups, each of which is optionally substituted with halogen(s) OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, where R_a and R_b independently are alkyl, unsaturated alkyl or aryl groups;

55 provided that R₁ is not -OH or a straight chain alkyl group where the second carbon of the chain is substituted with -OH or =O and R₁, R₄ and R₅ are not all methyl groups when R₂, R₃ and R₆ are all hydrogen;

(b) exposing said surface to a triggering event of photoradiation or a pH sufficient to activate the microorganism neutralizer, whereby said microorganisms are totally or partially prevented from replicating.

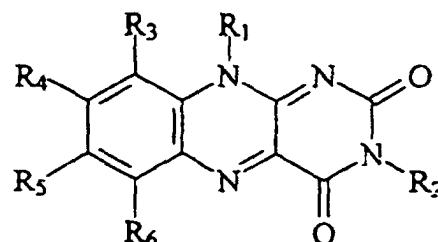
14. The method of claim 1 or 13, wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen; optionally substituted alcohol, polyalcohol, straight chain or cyclic saccharide, amino acid, ether, polyether, amine, polyamine, sulfate, phosphate, carbonyl, glycol, halogen selected from the group chlorine, bromine and iodine, aldehyde, ketone, carboxylic acid and ascorbate.

5
15. The method of claim 14, wherein said surface is a food surface, the surface of an animal carcass, a food-preparation surface or a surface of a bathing or washing vessel.

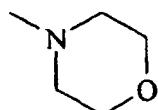
10
16. A fluid obtainable by the method of claim 3 and comprising biologically active protein, blood or blood constituents, and the microorganism neutralizer.

17. A blood product obtainable by the method of claim 3 and comprising the microorganism neutralizer.

15
18. A compound having the structure:



wherein R1, R2, R3, R4, R5 and R6 are, independently from one another, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, alcohol, amine, polyamine, sulfate, phosphate, halogen selected from the group consisting of chlorine, bromine and iodine, salts of the foregoing; and -NR^a-(CR^bR^c)_n-X wherein X is a halogen selected from the group consisting of chlorine, bromine and iodine, R^a, R^b and R^c are, independently of each other, selected from the group consisting of hydrogen, optionally substituted hydrocarbyl, and halogen selected from the group consisting of chlorine, bromine and iodine, and n is an integer from 0 to 20; provided that R1 is not -OH or a straight chain alkyl group where the second carbon of the chain is substituted with -OH or =O; and R1 is not a 2-, 3-, 4- or 5-carbon straight chain alkyl that terminates in -OH, -COH, or -H when R2, R3 and R6 are H, and R4 and R5 are CH₃; R1 is not -CH₂CH₂-(CHOH)₂-CH₃ or -CH₂CH₂(CHOH)₂-CH₂SO₄ or 1'-D-sorbityl or 1'-D-dulcetyl or 1'-D-rhamnityl or 1'-D,L-glyceryl or -CH₂-O-C(O)-CH₃ or CH₂-O-C(O)-CH₂CH₃ or 2',3',4',5'-di-O-isopropylidene-riboflavin or 8-aminoctyl when R2, R3 and R6 are H and R4 and R5 are CH₃; R1 is not 1'-D-sorbityl or 1'-D-dulcetyl when R4 and R5 are both chlorines and when R2, R3 and R6 are all hydrogens; R5 is not ethyl or chloro when R1 and R4 are methyl and R2, R3 and R6 are all hydrogens; R4 and R5 are not both methoxy or both tetramethylene when R1 is methyl and R2, R3 and R6 are all hydrogens; R2 is not -CH₂CH₂NH when R1, R4 and R5 are CH₃ and R3 and R6 are H; R2 is not



when R1, R4 and R5 are CH₃ and R3 and R6 are H; R5 is not chloro when R4 is methoxy and R1 is ethyl-2'-N-pyrrolidino and R2, R3 and R6 are hydrogen; R1 is not N,N-dimethylaminopropyl or N,N-diethylaminoethyl when R5 is chloro or methyl and R2, R3, R4 and R6 are hydrogen; R3 is not -NH(CH₂CH₂)Cl when R6 is -NH₂ and R1, R2, R4 and R5 are H; R1, R4 and R5 are not all methyl groups when all of R2, R3 and R6 are hydrogens; R1, R4, R5 and R2 are not all methyl groups when R3 and R6 are hydrogens; R2 is not carboxymethyl when R1, R4 and R5 are methyl and R3 and R6 are hydrogen; R4 is not -NH₂ when R1 and R5 are methyl and R2, R3 and R6 are all hydrogen; R1 is not a phenyl group when R4 and R5 are methyl and R2, R3 and R6 are all H; R1 is not methyl or N,N-dimethylaminopropyl when all of R2, R3, R4, R5 and R6 are hydrogen; R2, R4 and R5 are not all methyl when R1 is acetoxyethyl and R3 and R6 are hydrogen; R5 is not methyl when R1 is N,N-diethylaminoethyl and R2, R3, R4 and R6 are all hydrogen; R4 and R5 are not both chlorine when R1 is methyl and R2, R3 and R6 are

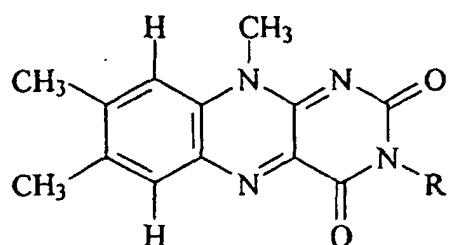
all hydrogen; R1 is not ethyl, β -chloroethyl, n-butyl, anilino, benzyl, phenyl, p-tolyl or p-anisyl when R5 is NH₂ and R2, R3, R4 and R6 are all hydrogen; and R4 is not chlorine when R1 is N,N-dimethylaminopropyl and R2, R3, R5 and R6 are all hydrogen.

- 5 19. The compound of claim 18, wherein one or a plurality of R1, R2, R3, R4, R5 and R6 are neither CH₃ nor H.
20. The compound of claim 19, wherein a plurality of R2, R3, R4, R5 and R6 are neither H nor CH₃.
- 10 21. The compound of claim 19, wherein a R1, R2, R3, R4, R5 and R6 that is neither CH₃ nor H is selected from the group consisting of:
- 15 alcohols, polyalcohols, straight chain or cyclic saccharides, amines, polyamines, sulfate groups, phosphate groups, ascorbate groups, alkyl chains optionally substituted with -OH at any position, glycols, ethers and polyethers,
- wherein the compound is soluble in water at a concentration of at least 10 μ M.
22. The compound of claim 21, wherein said R1, R2, R3, R4, R5 and R6 is selected from the group consisting of:
- 20 alcohols; polyalcohols; straight chain or cyclic saccharides; ether; polyether; amines; polyamines; sulfate groups; phosphate groups; ascorbate groups; alkyl chains optionally substituted with -OH at any position; glycols; and polyethers; and
- 25 wherein a plurality of R1, R2, R3, R4, R5 and R6 are neither CH₃ nor H.
23. The compound of claim 21, wherein the R1, R2, R3, R4, R5 and R6 is selected from the group consisting of:
- 30 alcohols; polyalcohols; straight chain or cyclic saccharides; amines and polyamines; sulfate groups; phosphate groups; ascorbate groups; alkyl chains optionally substituted with -OH at any position; glycols; ethers and polyethers;
- and wherein one of R1, R2, R3, R4, R5 and R6 is neither CH₃ nor H.
24. The compound of claim 22 or 23, wherein R1 is not CH₂-(CH₂OH)₃-CH₂OH.
- 35 25. The compound of claim 23, wherein the R1, R2, R3, R4, R5 or R6 that is neither H nor CH₃ is R2, R3, R4, R5 or R6.
26. The compound of claim 22, wherein R1 is -CH₂-(CH₂-OH)₃-CH₂OH.
- 40 27. The compound of claim 22 or 23, wherein R3 and R6 are H.
28. The compound of claim 19, wherein at least one of R1, R2, R3, R4, R5 and R6 contains a halogen selected from the group consisting of chlorine, bromine and iodine.
- 45 29. The compound of claim 28, wherein at least one of R1, R2, R3, R4, R5 and R6 is -(CH₂)_n-X, wherein n is either 1 or 2, and X is a halogen selected from the group consisting of chlorine, bromine and iodine.
30. The compound of claim 28, wherein at least one of the halogenated R1, R2, R3, R4, R5 and R6 is -NR(CH₂)_n-X, wherein R is hydrogen or straight chain alkyl group consisting of one to 6 carbon atoms, n is an integer from 0 to 6, and X is selected from the group consisting of chlorine, bromine and iodine.
- 50 31. The compound of claim 30, wherein R4 or R5 is -NR(CH₂)_n-X, wherein R is hydrogen or straight chain alkyl group consisting of one to 6 carbon atoms, n is an integer from 0 to 6, and X is selected from the group consisting of chlorine, bromine and iodine.
- 55 32. The compound of claim 18, wherein at least one of R1, R2, R3, R4, R5 and R6 are branched or unbranched C1 to C20 alkyl groups substituted with at least one -OH group.

33. The compound of claim 18 having the structure:

5

(a)

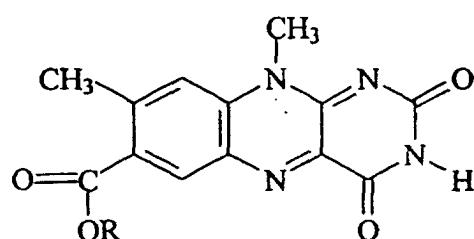


10

wherein R is selected from the group consisting of ascorbate, alcohol, polyalcohol, amine or polyamines, straight chain or cyclic saccharides, sulfates, phosphates, polyethylene glycols and polyethers; or

15

(b)



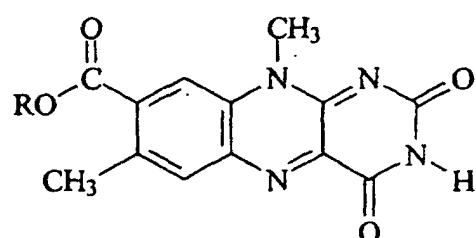
20

wherein R is selected from the group consisting of hydrogen and optionally substituted straight chain or branched alkyl having from 1 to 20 carbon atoms; or

30

35

(c)



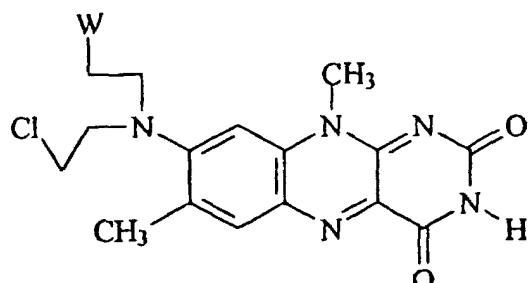
40

wherein R is selected from the group consisting of hydrogen and optionally substituted straight chain or branched alkyl having from 1 to 20 carbon atoms; or

45

50

(d)

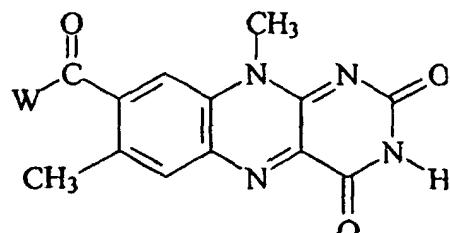


55

wherein W is selected from the group consisting of alcohols, polyalcohols, straight chain or cyclic saccharides, amines, polyamines, sulfate groups, phosphate groups, ascorbate groups, alkyl chains optionally substituted with -OH at any position, glycols, ethers and polyethers wherein the compound is soluble in water at a concentration

of at least 10 μM .

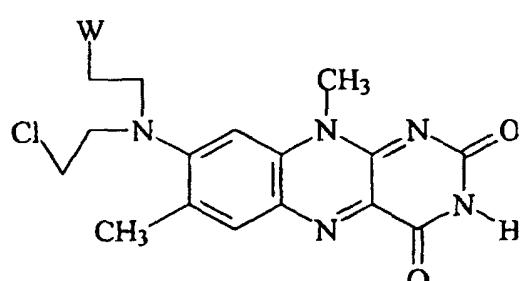
34. The compound of claim 18, wherein at least one of R1, R2, R3, R4, R5 and R6 are alkylating agents.
- 5 35. The compound of claim 18, wherein at least one of R1, R2, R3, R4, R5 and R6 are substituents that cause the compound to be substantially nonreactive to microorganisms at substantially neutral pH and active toward microorganism neutralization at the pH of the biological fluid.
- 10 36. A method of making a compound having structure:



wherein W is a group which makes the compound soluble in water at a concentration of at least 10 μM , comprising:

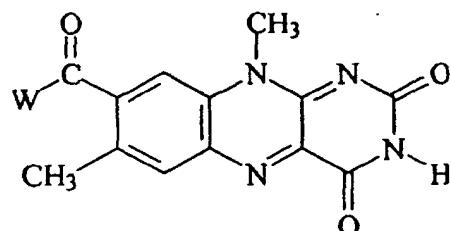
- 25
- (a) photolyzing carboxyriboflavin;
 - (b) reacting (a) with oxallylchloride;
 - (c) reacting (b) with a member of the group consisting of ascorbate, glucosamine, protected glucose derivatives, diethylene glycol and triethylene glycol.

- 30 37. A method of making a compound having the structure:



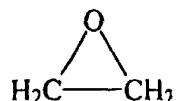
where W is a group which makes the compound soluble in water at a concentration of at least 10 μM , comprising:

- 45 (a) contacting



with sodium azide;

(b) reacting (a) with



10 and POCl₃.

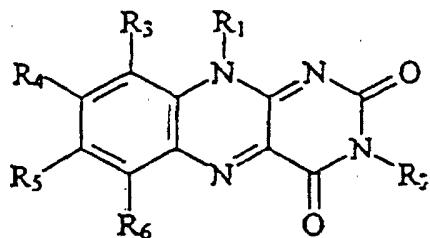
(c) reacting (b) with a group selected from: alcohols, polyalcohols, straight chain or cyclic saccharides, amines, polyamines, sulfate groups, phosphate groups, ascorbate groups, alkyl chains optionally substituted with -OH at any position, glycols, ethers and polyethers.

15

Patentansprüche

1. Verfahren zur Behandlung eines Fluids *in vitro*, um Mikroorganismen, die darin vorhanden sein können, ganz oder teilweise an einer Replikation zu hindern, wobei das Verfahren umfasst:

20 (a) die Zugabe zu dem Fluid von mindestens 1 µM eines Neutralisators für Mikroorganismen der Formel



35 in der R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Hydrocarbyl, Alkohol, Amin, Polyamin, Sulfat, Phosphat, Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, Salzen der vorstehenden; und -NR^a-(CR^bR^c)_n-X, in der X ein aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewähltes Halogen ist, R^a, R^b und R^c unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Hydrocarbyl und Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, und n eine ganze Zahl von 0 bis 20 ist; wobei eine ggfs. substituierte Hydrocarbylgruppe eine Gruppe ist, ausgewählt aus Alkyl, Alkenyl, Aikynyl, Ether, Polyether, Thioether, geradkettigen oder cyclischen Sacchariden, Ascorbat, Aminoalkyl-, Hydroxyalkyl-, Thioalkyl-, Aryl- und heterocyclischen Arylgruppen, Isoalloxazinmolekülen, Aminosäure, Polyalkohol, Glycol, carbocyclischen Ringen und Kombinationen solcher Gruppen, von denen jede ggfs. mit Halogen(en), OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b substituiert ist, wobei R_a und R_b unabhängig voneinander Alkyl-, ungesättigte Alkyl- oder Arylgruppen bedeuten; vorausgesetzt, dass R₁ nicht -OH oder eine geradkettige Alkylgruppe ist, wenn das zweite Kohlenstoffatom der Kette mit -OH oder =O substituiert ist, und R₁, R₄ und R₅ nicht alle Methylgruppen sind, wenn R₂, R₃ und R₆ alle Wasserstoff sind;

40

45

50

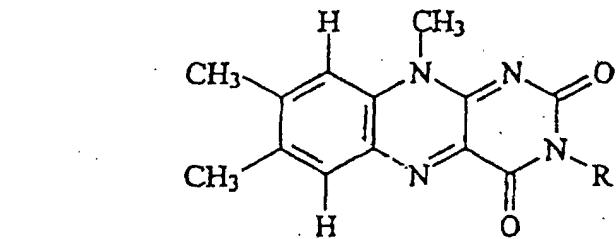
55

b) Exponieren des Fluids aus Schritt (a) an ein auslösendes Ereignis einer Lichtstrahlung oder eines pH, die bzw. der ausreicht, um den Mikroorganismenneutralisator zu aktivieren, wodurch die Mikroorganismen ganz oder teilweise an der Replikation gehindert werden.

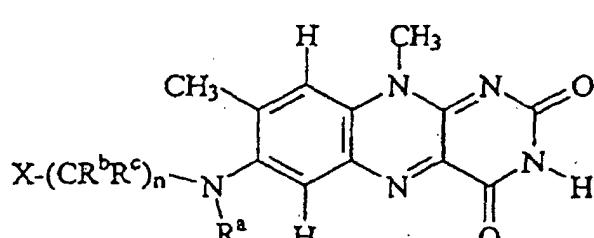
2. Verfahren nach Anspruch 1, bei dem das Fluid ein Lebensmittelprodukt, ein für den Verbrauch durch Menschen oder Tiere bestimmtes Getränk oder eine peritoneale Dialyselösung ist.

3. Verfahren nach Anspruch 1, bei dem das Fluid eine oder mehrere Komponenten enthält, ausgewählt aus der aus Protein, Blut und Blutbestandteilen bestehenden Gruppe.
 4. Verfahren nach Anspruch 3, bei dem R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Alkohol, geradkettigem oder cyclischem Saccharid, Aminosäure, Amin, Polyamin, Polyether, Polyalkohol, Sulfat, Phosphat, Carbonyl, Glycol, Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, Aldehyd, Keton, Carbonsäure und Ascorbat.
 5. Verfahren nach Anspruch 3, bei dem das auslösende Ereignis eine Lichtstrahlung ist, die ausreicht, um den Mikroorganismenneutralisator zu aktivieren.
 6. Verfahren nach Anspruch 3, bei dem das auslösende Ereignis ein pH ist, der ausreicht, um den Mikroorganismen-neutralisator zu aktivieren.
 7. Verfahren nach Anspruch 3, bei dem die Mikroorganismen ausgewählt werden aus der Gruppe, bestehend aus HIV-Viren, Hepatitisviren, Sindbisviren, Cytomegalovirus, dem Virus der vesikulären Stomatitis, Herpes simplex-Viren, Vaccinia-Virus, humanen T-lymphotropen Retroviren, HTLV-III, Lymphadenopathia-Virus LAV/IDAV, Parovirus, dem durch Transfusionen übertragenen Virus (TT-Virus), Epstein-Barr-Virus, Bakteriophagen ΦX174, Φ6, λ, R17, T₄, T₂, *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *L. monocytogenes*, *E. coli*, *K. pneumoniae* und *S. marcescens*.
 8. Verfahren nach Anspruch 3, bei dem der Mikroorganismenneutralisator ausgewählt wird aus

25 (a)



35 in der R ausgewählt wird aus der Gruppe, bestehend aus Ascorbat, Alkohol, Polyalkohol, Amin, Polyamin, gerad-

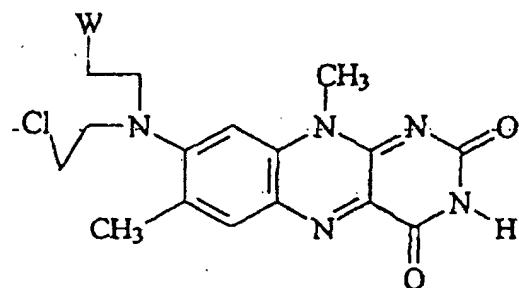


50 in der X ein aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewähltes Halogen ist, R^a, R^b und R^c unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Hydrocarbyl und Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, und n eine ganze Zahl von 0 bis 20 ist:
55

(c)

5

10



15 in der W eine Gruppe ist, die den Neutralisator bei einer Konzentration von mindestens 10 µM in Wasser löslich macht.

9. Verfahren nach Anspruch 3, bei dem das Fluid Plättchen, rote Blutkörperchen, Serum oder Plasma umfasst, das vom Vollblut getrennt ist.

20 10. Verfahren nach Anspruch 3, bei dem der Mikroorganismenneutralisator einem Antikoagulans zugesetzt und das Antikoagulans zum Fluid gegeben wird.

25 11. Verfahren nach Anspruch 3, bei dem dem Fluid ein Antioxidans zugesetzt wird, ehe das Fluid dem auslösenden Ereignis ausgesetzt wird.

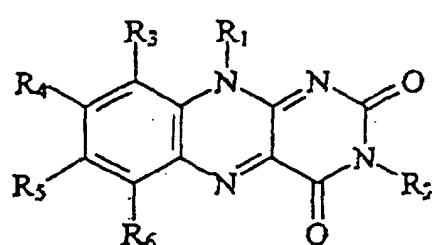
12. Verfahren nach Anspruch 3, bei dem dann, wenn der Mikroorganismenneutralisator photolytische Produkte erzeugt, die photolytischen Produkte für Menschen oder Tiere weniger toxisch sind als Porphyrin.

30 13. Verfahren, bei dem Mikroorganismen auf einer Oberfläche ganz oder teilweise an der Replikation gehindert werden, umfassend:

(a) das Aufbringen von mindestens 1 µM einer Verbindung der Formel

35

40



45 in der R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Hydrocarbyl, Alkohol, Amin, Polyamin, Sulfat, Phosphat, Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, Salzen der vorstehenden;

50 und -NR^a-(CR^bR^c)_n-X, in der X ein aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewähltes Halogen ist, R^a, R^b und R^c unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggfs. substituiertem Hydrocarbyl und Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, und n eine ganze Zahl von 0 bis 20 ist;

wobei eine ggfs. substituierte Hydrocarbylgruppe eine Gruppe ist, ausgewählt aus Alkyl, Alkenyl, Alkynyl, Ether, Polyether, Thioether, geradkettigen oder cyclischen Sacchariden, Ascorbat, Aminoalkyl-, Hydroxyalkyl-, Thioalkyl-, Aryl- und heterocyclischen Arylgruppen, Isoalloxazinmolekülen, Aminosäure, Polyalkohol, Glycol, carbocyclischen Ringen und Kombinationen solcher Gruppen, von denen jede ggfs. mit Halogen(en), OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b substituiert ist, wobei R_a und R_b unabhängig voneinander Alkyl-, ungesättigte Alkyl- oder Arylgruppen bedeuten;

vorausgesetzt, dass R₁ nicht -OH oder eine geradkettige Alkylgruppe ist, wenn das zweite Kohlenstoffatom der Kette mit -OH oder =O substituiert ist, und R₁, R₄ und R₅ nicht alle Methylgruppen sind, wenn R₂, R₃ und R₆ alle Wasserstoff sind;

- 5 b) Exponieren der Oberfläche an ein auslösendes Ereignis einer Lichtstrahlung oder eines pH, die bzw. der ausreicht, um den Mikroorganismenneutralisator zu aktivieren, wodurch die Mikroorganismen ganz oder teilweise an der Replikation gehindert werden.

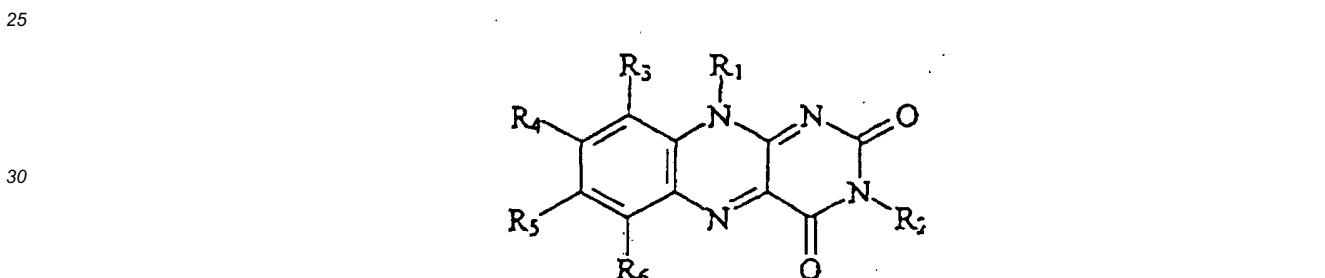
10 14. Verfahren nach Anspruch 1 oder 13, bei dem R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggf. substituiertem Alkohol, Polyalkohol, geradkettigem oder cyclischem Saccharid, Aminosäure, Ether, Polyether, Amin, Polyamin, Sulfat, Phosphat, Carbonyl, Glycol, Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, Aldehyd, Keton, Carbonsäure und Ascorbat.

15 15. Verfahren nach Anspruch 14, bei dem die Oberfläche die Oberfläche eines Lebensmittels, eines Tierkadavers, eine Oberfläche zur Zubereitung von Lebensmitteln oder eine Oberfläche eines Bade- oder Waschgefäßes ist.

20 16. Fluid, das durch das Verfahren von Anspruch 3 erhältlich ist und biologisch aktives Protein, Blut oder Blutbestandteile und den Mikroorganismenneutralisator umfasst.

25 17. Blutprodukt, das durch das Verfahren von Anspruch 3 erhältlich ist und den Mikroorganismenneutralisator umfasst.

18. Verbindung der Struktur



in der R₁, R₂, R₃, R₄, R₅ und R₆ jeweils unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggf. substituiertem Hydrocarbyl, Alkohol, Amin, Polyamin, Sulfat, Phosphat, Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, Salzen der vorstehenden; und -NR^a-(CR^bR^c)_n-X, in der X ein aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewähltes Halogen ist, R^a, R^b und R^c unabhängig voneinander ausgewählt werden aus der Gruppe, bestehend aus Wasserstoff, ggf. substituiertem Hydrocarbyl und Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, und n eine ganze Zahl von 0 bis 20 ist;

vorausgesetzt,

R₁ ist nicht -OH oder eine geradkettige Alkylgruppe, wenn das zweite Kohlenstoffatom der Kette mit -OH oder =O substituiert ist; und R₁ ist kein geradkettiges Alkyl mit 2, 3, 4 oder 5 Kohlenstoffatomen, das mit -OH, -COH oder -H endet, wenn R₂, R₃ und R₆ H sind und R₄ und R₅ CH₃ sind;

R₁ ist nicht -CH₂CH₂-(CHOH)₂-CH₃ oder -CH₂CH₂(CHOH)₂-CH₂SO₄ oder 1'-D-Sorbityl oder 1'-D-Dulcetyl oder 1'-D-Rhamnityl oder 1'-D,L-Glyceryl oder -CH₂-O-C(O)-CH₃ oder CH₂-O-C(O)-CH₂CH₃ oder 2',3',4',5'-Di-O-isopropylidenriboflavin oder 8-Aminoocetyl, wenn R₂, R₃ und R₆ H sind und R₄ und R₅ CH₃ sind;

R₁ ist nicht 1'-D-Sorbityl oder 1'-D-Dulcetyl, wenn R₄ und R₅ beide Chloratome sind und wenn R₂, R₃ und R₆ alle Wasserstoffatome sind;

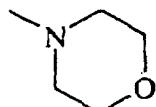
R₅ ist nicht Ethyl oder Chlor, wenn R₁ und R₄ Methyl sind und R₂, R₃ und R₆ alle Wasserstoffatome sind;

R₄ und R₅ sind nicht beide Methoxy oder beide Tetramethylen, wenn R₁ Methyl ist und R₂, R₃ und R₆ alle Wasserstoffatome sind;

R₂ ist nicht -CH₂CH₂NH, wenn R₁, R₄ und R₅ CH₃ sind und R₃ und R₆ H sind;

R₂ ist nicht

5



wenn R₁, R₄ und R₅ CH₃ sind und R₃ und R₆ H sind;
 R₅ ist nicht Chlor, wenn R₄ Methoxy ist und R₁ Ethyl-2'-N-pyrrolidino ist und R₂, R₃ und R₆ Wasserstoff sind;
 R₁ ist nicht N,N-Dimethylaminopropyl oder N,N-Diethylaminoethyl, wenn R₅ Chlor oder Methyl ist und R₂, R₃, R₄ und R₆ Wasserstoff sind;
 R₃ ist nicht -NH(CH₂CH₂)Cl, wenn R₆ -NH₂ ist und R₁, R₂, R₄ und R₅ H sind;
 R₁, R₄ und R₅ sind nicht alle Methylgruppen, wenn R₂, R₃ und R₆ alle Wasserstoffatome sind;
 R₁, R₄, R₅ und R₂ sind nicht alle Methylgruppen, wenn R₃ und R₆ Wasserstoffatome sind;
 R₂ ist nicht Carboxymethyl, wenn R₁, R₄ und R₅ Methyl sind und R₃ und R₆ Wasserstoff sind;
 R₄ ist nicht -NH₂, wenn R₁ und R₅ Methyl sind und R₂, R₃ und R₆ alle Wasserstoff sind;
 R₁ ist keine Phenylgruppe, wenn R₄ und R₅ Methyl sind und R₂, R₃ und R₆ alle H sind;
 R₁ ist nicht Methyl oder N,N-Dimethylaminoethyl, wenn R₂, R₃, R₄, R₅ und R₆ alle Wasserstoff sind;
 R₂, R₄ und R₅ sind nicht alle Methyl, wenn R₁ Acetoxyethyl ist und R₃ und R₆ Wasserstoff sind;
 R₅ ist nicht Methyl, wenn R₁ N,N-Diethylaminoethyl ist und R₂, R₃, R₄ und R₆ alle Wasserstoff sind;
 R₄ und R₅ sind nicht beide Chlor, wenn R₁ Methyl ist und R₂, R₃ und R₆ alle Wasserstoff sind;
 R₁ ist nicht Ethyl, β-Chlorethyl, n-Butyl, Anilino, Benzyl, Phenyl, p-Tolyl oder p-Anisyl, wenn R₅ NH₂ ist und R₂, R₃, R₄ und R₆ alle Wasserstoff sind;
 und R₄ ist nicht Chlor, wenn R₁ N,N-Dimethylaminopropyl ist und R₂, R₃, R₅ und R₆ alle Wasserstoff sind.

25 19. Verbindung nach Anspruch 18, bei der eines oder eine Vielzahl von R₁, R₂, R₃, R₄, R₅ und R₆ weder CH₃ noch H ist.

20. Verbindung nach Anspruch 19, bei der eine Vielzahl von R₂, R₃, R₄, R₅ und R₆ weder H noch CH₃ sind.

30 21. Verbindung nach Anspruch 19, in der ein R₁, R₂, R₃, R₄, R₅ und R₆, das weder CH₃ noch H ist, ausgewählt wird aus der Gruppe, bestehend aus Alkoholen, Polyalkoholen, geradkettigen oder cyclischen Sacchariden, Aminen, Polyaminen, Sulfatgruppen, Phosphatgruppen, Ascorbatgruppen, Alkylketten, die an einer beliebigen Position ggfs. mit -OH substituiert sind, Glycolen, Ethern und Polyethern, wobei die Verbindung bei einer Konzentration von mindestens 10 µm in Wasser löslich ist.

35 22. Verbindung nach Anspruch 21, in der das R₁, R₂, R₃, R₄, R₅ und R₆ ausgewählt wird aus der Gruppe, bestehend aus Alkoholen, Polyalkoholen, geradkettigen oder cyclischen Sacchariden, Ethem, Polyether, Aminen, Polyaminen, Sulfatgruppen, Phosphatgruppen, Ascorbatgruppen, Alkylketten, die an einer beliebigen Position ggfs. mit -OH substituiert sind, Glycolen, Ethern und Polyethem, und in der eine Vielzahl von R₁, R₂, R₃, R₄, R₅ und R₆ weder CH₃ noch H sind.

40 23. Verbindung nach Anspruch 21, in der das R₁, R₂, R₃, R₄, R₅ und R₆ ausgewählt wird aus der Gruppe, bestehend aus Alkoholen, Polyalkoholen, geradkettigen oder cyclischen Sacchariden, Aminen und Polyaminen, Sulfatgruppen, Phosphatgruppen, Ascorbatgruppen, Alkylketten, die an einer beliebigen Position ggfs. mit -OH substituiert sind, Glycolen, Ethern und Polyethem, und in der eines von R₁, R₂, R₃, R₄, R₅ und R₆ weder CH₃ noch H ist.

45 24. Verbindung nach Anspruch 22 oder 23, in der R₁ nicht CH₂-(CH₂OH)₃-CH₂OH ist.

50 25. Verbindung nach Anspruch 23, in der das R₁, R₂, R₃, R₄, R₅ oder R₆, das weder H noch CH₃ ist, R₂, R₃, R₄, R₅ oder R₆ ist.

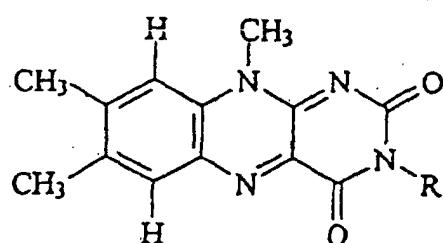
55 26. Verbindung nach Anspruch 22, in der R₁ -CH₂-(CH₂-OH)₃-CH₂OH ist.

27. Verbindung nach Anspruch 22 oder 23, in der R₃ und R₆ H sind.

55 28. Verbindung nach Anspruch 19, in der mindestens eines von R₁, R₂, R₃, R₄, R₅ und R₆ ein Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehenden Gruppe, enthält.

29. Verbindung nach Anspruch 28, in der mindestens eines von R₁, R₂, R₃, R₄, R₅ und R₆ -(CH₂)_n-X ist, in der n entweder 1 oder 2 ist und X ein Halogen, ausgewählt aus der aus Chlor, Brom und Iod bestehende Gruppe, ist.
- 5 30. Verbindung nach Anspruch 28, in der mindestens eines der halogenierten R₁, R₂, R₃, R₄, R₅ und R₆ -NR(CH₂)_n-X ist, in der R Wasserstoff oder eine geradkettige Alkylgruppe, bestehend aus 1 bis 6 Kohlenstoffatomen, bedeutet, n eine ganze Zahl von 0 bis 6 ist und X aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewählt ist.
- 10 31. Verbindung nach Anspruch 30, in der R₄ oder R₅ -NR(CH₂)_n-X ist, in der R Wasserstoff oder eine geradkettige Alkylgruppe, bestehend aus 1 bis 6 Kohlenstoffatomen, bedeutet, n eine ganze Zahl von 0 bis 6 ist und X aus der aus Chlor, Brom und Iod bestehenden Gruppe ausgewählt ist.
- 15 32. Verbindung nach Anspruch 18, in der mindestens eines von R₁, R₂, R₃, R₄, R₅ und R₆ eine verzweigte oder unverzweigte C₁-C₂₀-Alkylgruppe, die mit mindestens einer -OH-Gruppe substituiert ist, ist.
- 15 33. Verbindung nach Anspruch 18 mit der Struktur:

(a)

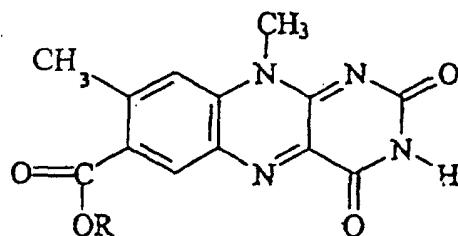


20

25

in der R ausgewählt wird aus der Gruppe, bestehend aus Ascorbat, Alkohol, Polyalkohol, Amin oder Polyaminen, geradkettigen oder cyclischen Sacchariden, Sulfaten, Phosphaten, Polyethylenglyolen und Polyethern; oder

(b)

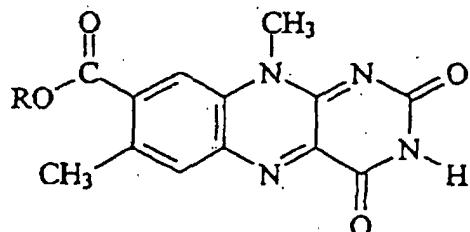


30

35

in der R ausgewählt wird aus der Gruppe, bestehend aus Wasserstoff und ggf. substituiertem geradkettigem oder verzweigtem Alkyl mit 1 bis 20 Kohlenstoffatomen; oder

(c)



45

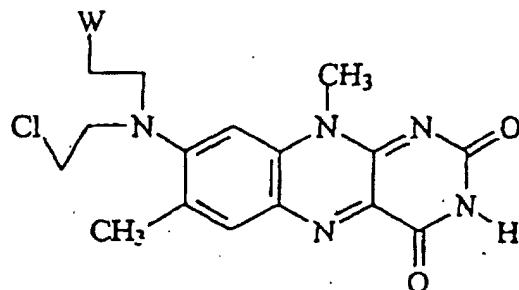
50

in der R ausgewählt wird aus der Gruppe, bestehend aus Wasserstoff und ggf. substituiertem geradkettigem oder verzweigtem Alkyl mit 1 bis 20 Kohlenstoffatomen; oder

55

5

(d)



10

in der W ausgewählt wird aus der Gruppe, bestehend aus Alkoholen, Polyalkoholen, geradkettigen oder cyclischen Sacchariden, Aminen, Polyaminen, Sulfatgruppen, Phosphatgruppen, Ascorbatgruppen, Alkylketten, die an einer beliebigen Position ggfs. mit -OH substituiert sind, Glycolen, Ethern und Polyethern, wobei die Verbindung bei einer Konzentration von mindestens $10 \mu\text{M}$ in Wasser löslich ist.

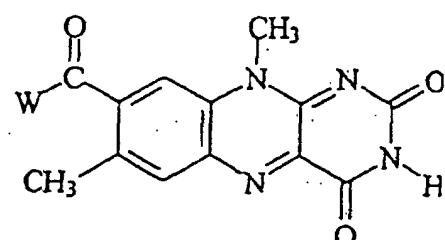
- 15
34. Verbindung nach Anspruch 18, in der mindestens eines von $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5$ und R_6 Alkylierungsmittel sind.
- 20 35. Verbindung nach Anspruch 18, in der mindestens eines von $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5$ und R_6 Substituenten sind, die dafür sorgen, dass die Verbindung bei einem im Wesentlichen neutralen pH im Wesentlichen nicht mit Mikroorganismen reaktiv ist und beim pH des biologischen Fluids neutralisierend auf Mikroorganismen wirkt.

25

36. Verfahren zur Herstellung einer Verbindung der Struktur

25

30



35

in der W eine Gruppe ist, die die Verbindung bei einer Konzentration von mindestens $10 \mu\text{M}$ in Wasser löslich macht, umfassend

40

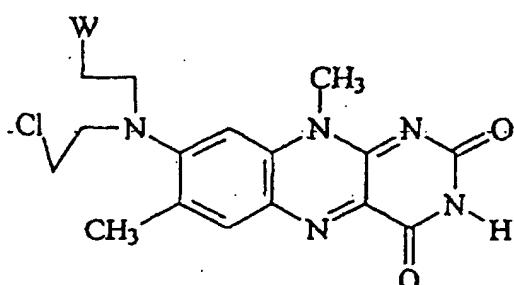
- (a) die Photolyse von Carboxyriboflavin;
- (b) das Umsetzen von (a) mit Oxallylchlorid;
- (c) das Umsetzen von (b) mit einer Komponente aus der Gruppe, bestehend aus Ascorbat, Glucosamin, geschützten Glucosederivaten, Diethylenglycol und Triethylenglycol.

45

37. Verfahren zur Herstellung einer Verbindung der Struktur

50

55



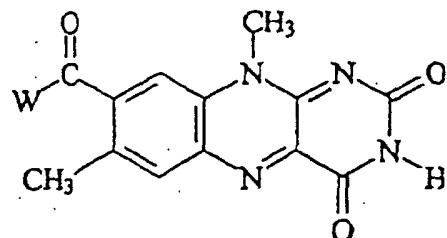
in der W eine Gruppe ist, die die Verbindung bei einer Konzentration von mindestens $10 \mu\text{M}$ in Wasser löslich macht; umfassend

(a) das In-Kontakt-Bringen von

5

10

15

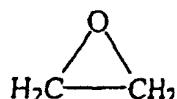


mit Natriumazid;

20

(b) das Umsetzen von (a) mit

25



und POCl_3 ;

30

(c) das Umsetzen von (b) mit einer Gruppe, ausgewählt aus Alkoholen, Polyalkoholen, geradkettigen oder cyclischen Sacchariden, Aminen, Polyaminen, Sulfatgruppen, Phosphatgruppen, Ascorbatgruppen, Alkylketten, die ggfs. an einer beliebigen Position mit -OH substituiert sind, Glycolen, Ethern und Polyethern.

Revendications

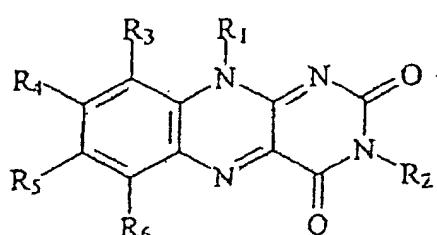
35

1. Procédé pour traiter un fluide in vitro pour empêcher totalement ou partiellement des micro-organismes qui peuvent être présents dans celui-ci de se répliquer, ledit procédé comprenant :

40

(a) l'addition audit fluide d'au moins $1 \mu\text{M}$ d'un neutralisant de micro-organismes de formule :

45



50

dans laquelle R1, R2, R3, R4, R5 et R6 sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué, alcool, amine, polyamine, sulfate, phosphate, halogène choisi dans le groupe constitué du chlore, du bromé et de l'iode, sels des précédents ; et $-\text{NR}^a-(\text{CR}^b\text{R}^c)_n-\text{X}$ où X est un halogène choisi dans le groupe constitué du chlore, du bromé et de l'iode, R^a , R^b et R^c sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué et halogène choisi dans le groupe constitué du chlore, du bromé et de l'iode, et n est un nombre entier de 0 à 20 ;

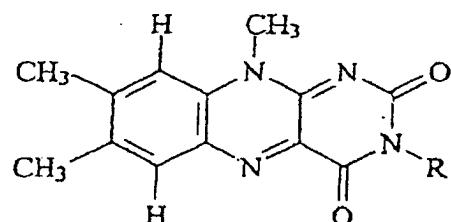
où un groupe hydrocarbyle éventuellement substitué est un groupe choisi parmi alkyle, alcényle, alcynyle, éther, polyéther, thioéther, saccharides à chaîne linéaire ou cycliques, ascorbate, aminoalkyle, hydroxyalkyle, thioalkyle, aryle et aryle hétérocyclique, molécules d'iso-alloxazine, aminoacide, polyol, glycol, cycles carbocycliques et combinaisons de tels groupes, chacun d'eux étant éventuellement substitué par un ou des halogènes, OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, où R_a et R_b sont indépendamment des groupes alkyle, alkyle insaturé ou aryle ;

avec la condition que R1 ne soit pas -OH ou un groupe alkyle à chaîne linéaire quand le second atome de carbone de la chaîne est substitué par -OH ou =O et que R1, R4 et R5 ne soient pas tous des groupes méthyle quand R2, R3 et R6 sont tous de l'hydrogène ;

(b) l'exposition du fluide de l'étape (a) à un événement déclencheur de photoradiation ou d'un pH suffisant pour activer le neutralisant de micro-organismes, moyennant quoi lesdits micro-organismes sont totalement ou partiellement empêchés de se répliquer.

- 15 2. Procédé selon la revendication 1, dans lequel ledit fluide est un produit alimentaire, une boisson destinée à la consommation humaine ou animale ou une solution de dialyse péritoneale.
- 20 3. Procédé selon la revendication 1, dans lequel ledit fluide contient un ou plusieurs composants choisis dans le groupe constitué de protéines, sang et constituants du sang.
- 25 4. Procédé selon la revendication 3, dans lequel R1, R2, R3, R4, R5 et R6 sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, alcool éventuellement substitué, saccharide à chaîne linéaire ou cyclique, aminoacide, amine, polyamine, polyéther, polyol, sulfate, phosphate, carbonyle, glycol, halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, aldéhyde, cétone, acide carboxylique et ascorbate.
- 30 5. Procédé selon la revendication 3, dans lequel ledit événement déclencheur est une photoradiation suffisante pour activer le neutralisant de micro-organismes.
- 35 6. Procédé selon la revendication 3, dans lequel ledit événement déclencheur est un pH suffisant pour activer le neutralisant de micro-organismes.
7. Procédé selon la revendication 3, dans lequel lesdits micro-organismes sont choisis dans le groupe constitué des virus du VIH, virus de l'hépatite, virus Sindbis, cytomégalovirus, virus de la stomatite vésiculeuse, virus de l'herpès, virus de la vaccine, rétrovirus T-lymphotropes humains, HTLV-III, virus de la lymphadénopathie LAV/IDAV, parvovirus, virus transmis par transfusion (TT), virus d'Epstein-Barr, bactériophages ΦX174, Φ6, λ, R17, T₄, T₂, P. aeruginosa, S. aureus, S. epidermidis, L. monocytogenes, E. coli, K. pneumoniae et S. marcescens.
- 40 8. Procédé selon la revendication 3, dans lequel le neutralisant de micro-organismes est choisi parmi

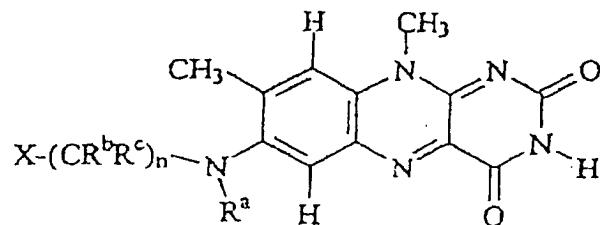
(a)



où R est choisi dans le groupe constitué d'ascorbate, alcool, polyol, amine, polyamine, saccharides à chaîne linéaire ou cycliques, sulfates, phosphates, polyéthylèneglycols et polyéthers ;

5

(b)



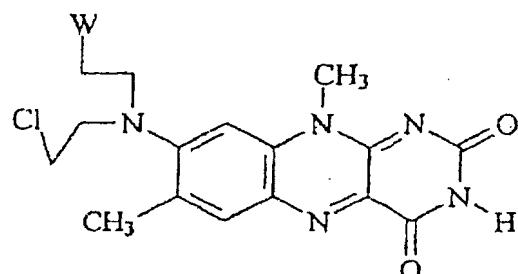
10

où X est un halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, R^a , R^b et R^c sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué et halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, et n est un nombre entier de 0 à 20 ; ou

15

20

(c)



25

où W est un groupe qui rend le neutralisant soluble dans l'eau à une concentration d'au moins $10 \mu M$.

9. Procédé selon la revendication 3, dans lequel ledit fluide comprend des plaquettes, des globules rouges, du sérum ou du plasma séparés à partir de sang entier.

10. Procédé selon la revendication 3, dans lequel ledit neutralisant de micro-organismes est ajouté à un anticoagulant et ledit anticoagulant est ajouté audit fluide.

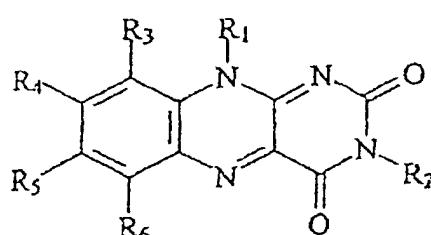
11. Procédé selon la revendication 3, dans lequel un antioxydant est ajouté audit fluide avant l'exposition dudit fluide audit événement déclencheur.

12. Procédé selon la revendication 3, dans lequel, si ledit neutralisant de micro-organismes produit des produits photolytiques, les produits photolytiques sont moins toxiques qu'une porphyrine pour les humains ou les animaux.

13. Procédé pour empêcher totalement ou partiellement la réPLICATION de micro-organismes sur une surface, comprenant :

45 (a) l'application sur ladite surface d'au moins $1 \mu M$ d'un composé de formule :

50



55

dans laquelle R_1 , R_2 , R_3 , R_4 , R_5 et R_6 sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué, alcool, amine, polyamine, sulfate, phosphate,

halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, sels des précédents ; et $-NR^a-(CR^bR^c)_n-X$ où X est un halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, R^a, R^b et R^c sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué et halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, et n est un nombre entier de 0 à 20 ;

où un groupe hydrocarbyle éventuellement substitué est un groupe choisi parmi alkyle, alcényle, alcynyle, éther, polyéther, thioéther, saccharides à chaîne linéaire ou cycliques, ascorbate, aminoalkyle, hydroxylalkyle, thioalkyle, aryle et aryle hétérocyclique, molécules d'iso-alloxazine, aminoacide, polyol, glycol, cycles carbocycliques et combinaisons de tels groupes, chacun d'eux étant éventuellement substitué par un ou des halogènes, OH, SH, NH₂, COH, CO₂H, OR_a, SR_a, NR_aR_b, CONR_aR_b, où R_a et R_b sont indépendamment des groupes alkyle, alkyle insaturé ou aryle ;

avec la condition que R1 ne soit pas -OH ou un groupe alkyle à chaîne linéaire quand le second atome de carbone de la chaîne est substitué par -OH ou =O et que R1, R4 et R5 ne soient pas tous des groupes méthyle quand R2, R3 et R6 sont tous de l'hydrogène ;

(b) l'exposition du fluide de l'étape (a) à un événement déclencheur de photoradiation ou d'un pH suffisant pour activer le neutralisant de micro-organismes, moyennant quoi lesdits micro-organismes sont totalement ou partiellement empêchés de se répliquer.

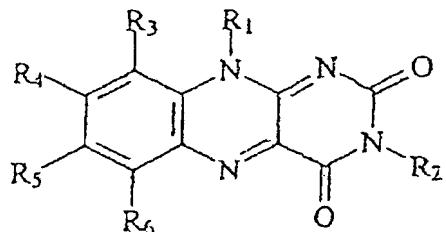
14. Procédé selon la revendication 1 ou 13, dans lequel R1, R2, R3, R4, R5 et R6 sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, alcool éventuellement substitué, saccharide à chaîne linéaire ou cyclique, aminoacide, amine, polyamine, polyéther, polyol, sulfate, phosphate, carbonyle, glycol, halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, aldéhyde, cétone, acide carboxylique et ascorbate.

15. Procédé selon la revendication 14, dans lequel ladite surface est la surface d'un aliment, la surface d'une carcasse d'animal, une surface de préparation d'aliments ou la surface d'une cuve de bain ou de lavage.

16. Fluide pouvant être obtenu par le procédé selon la revendication 3 et comprenant une protéine biologiquement active, du sang ou des constituants du sang et le neutralisant de micro-organismes.

17. Produit sanguin pouvant être obtenu par le procédé selon la revendication 3 et comprenant le neutralisant de micro-organismes.

18. Composé ayant la structure :



dans laquelle R1, R2, R3, R4, R5 et R6 sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué, alcool, amine, polyamine, sulfate, phosphate, halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, sels des précédents ;

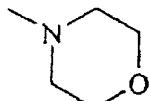
et $-NR^a-(CR^bR^c)_n-X$ où X est un halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, R^a, R^b et R^c sont choisis, indépendamment les uns des autres, dans le groupe constitué d'hydrogène, hydrocarbyle éventuellement substitué et halogène choisi dans le groupe constitué du chlore, du brome et de l'iode, et n est un nombre entier de 0 à 20 ;

avec la condition que R1 ne soit pas -OH ou un groupe alkyle à chaîne linéaire quand le second atome de carbone de la chaîne est substitué par -OH ou =O ; et que R1 ne soit pas un alkyle à chaîne linéaire ayant 2, 3, 4 ou 5 atomes de carbone qui se termine par -OH, -COH ou -H quand R2, R3 et R6 sont H, et R4 et R5 sont CH₃ ; que R1 ne soit pas -CH₂CH₂-(CHOH)₂-CH₃ ou -CH₂CH₂(CHOH)₂-CH₂SO₄ ou 1'-D-sorbityle ou 1'-D-dulcite ou 1'-D-rhamnityle ou 1'-D,L-glycéryle ou -CH₂-O-C(O)-CH₃ ou CH₂-O-C(O)-CH₂CH₃ ou 2',3',4',5'-di-O-isopropylidèneri-

boflavine ou 8-amino-octyle quand R2, R3 et R6 sont H et que R4 et R5 sont CH₃ ; que R1 ne soit pas 1'-D-sorbityle ou 1'-D-dulcitle quand R4 et R5 sont tous les deux des atomes de chlore et que R2, R3 et R6 sont tous des hydrogènes ; que R5 ne soit pas éthyle ou chloro quand R1 et R4 sont méthyle et que R2, R3 et R6 sont tous des hydrogènes ; que R4 et R5 ne soient pas tous les deux méthoxy ou tous les deux tétraméthylène quand R1 est méthyle et que R2, R3 et R6 sont tous des hydrogènes ; que R2 ne soit pas -CH₂CH₂NH quand R1, R4 et R5 sont CH₃ et que R3 et R6 sont H ; que R2 ne soit pas

5

10



quand R1, R4 et R5 sont CH₃ et que R3 et R6 sont H ; que R5 ne soit pas chloro quand R4 est méthoxy et que R1 est éthyl-2'-N-pyrrolidino et que R2, R3 et R6 sont l'hydrogène ; que R1 ne soit pas N,N-diméthylaminopropyle ou N,N-diéthylaminoéthyle quand R5 est chloro ou méthyle et que R2, R3, R4 et R6 sont l'hydrogène ; que R3 ne soit pas -NH(CH₂CH₂)Cl quand R6 est -NH₂ et que R1, R2, R4 et R5 sont H ; que R1, R4 et R5 ne soient pas tous des groupes méthyle quand R2, R3 et R6 sont tous des hydrogènes ; que R1, R4, R5 et R2 ne soient pas tous des groupes méthyle quand R3 et R6 sont des hydrogènes ; que R2 ne soit pas carboxyméthyle quand R1, R4 et R5 sont méthyle et que R3 et R6 sont des hydrogènes ; que R4 ne soit pas -NH₂ quand R1 et R5 sont méthyle et que R2, R3 et R6 sont tous des hydrogènes ; que R1 ne soit pas un groupe phényle quand R4 et R5 sont méthyle et que R2, R3 et R6 sont tous H ; que R1 ne soit pas méthyle ou N,N-diméthylaminoéthyle quand R2, R3, R4, R5 et R6 sont tous de l'hydrogène ; que R2, R4 et R5 ne soient pas tous méthyle quand R1 est acétoxyéthyle et que R3 et R6 sont de l'hydrogène ; que R5 ne soit pas méthyle quand R1 est N,N-diéthylaminoéthyle et que R2, R3, R4 et R6 sont tous de l'hydrogène ; que R4 et R5 ne soient pas tous les deux un atome de chlore quand R1 est méthyle et que R2, R3 et R6 sont tous de l'hydrogène ; que R1 ne soit pas éthyle, β-chloroéthyle, n-butyle, anilino, benzyle, phényle, p-tolylique ou p-anisyle quand R5 est NH₂ et que R2, R3, R4 et R6 sont tous de l'hydrogène ; et que R4 ne soit pas un atome de chlore quand R1 est N,N-diméthylaminopropyle et que R2, R3, R5 et R6 sont tous de l'hydrogène.

30

19. Composé selon la revendication 18, dans lequel un ou une pluralité de R1, R2, R3, R4, R5 et R6 ne sont ni CH₃ ni H.

20. Composé selon la revendication 19, dans lequel une pluralité de R2, R3, R4, R5 et R6 ne sont ni H ni CH₃.

35 21. Composé selon la revendication 19, dans lequel un R1, R2, R3, R4, R5 et R6 qui n'est ni CH₃ ni H est choisi dans le groupe constitué de :

alcools, polyols, saccharides à chaîne linéaire ou cycliques, amines, polyamines, groupes sulfates, groupes phosphates, groupes ascorbates, chaînes alkyle éventuellement substituées par -OH en une position quelconque, glycols, éthers et polyéthers,

ledit composé étant soluble dans l'eau à une concentration d'au moins 10 µM.

45 22. Composé selon la revendication 21, dans lequel ledit R1, R2, R3, R4, R5 et R6 est choisi dans le groupe constitué de :

alcools ; polyols ; saccharides à chaîne linéaire ou cycliques ; éther ; polyéther ; amine ; polyamine ; groupes sulfates ; groupes phosphates ; groupes ascorbates ; chaînes alkyle éventuellement substituées par -OH en une position quelconque ; glycols et polyéthers ; et

50

dans lequel une pluralité de R1, R2, R3, R4, R5 et R6 ne sont ni CH₃ ni H.

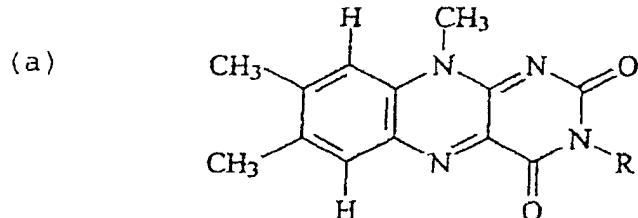
23. Composé selon la revendication 21, dans lequel le R1, R2, R3, R4, R5 et R6 est choisi dans le groupe constitué de :

55 alcools ; polyols ; saccharides à chaîne linéaire ou cycliques ; amines et polyamines ; groupes sulfates ; groupes phosphates ; groupes ascorbates ; chaînes alkyle éventuellement substituées par -OH en une position quelconque ; glycols ; éthers et polyéthers ;

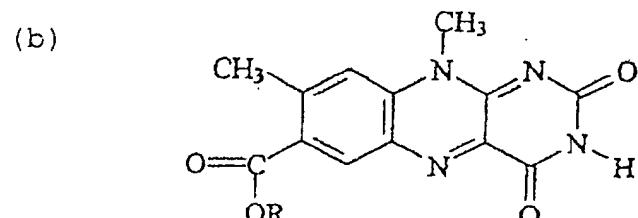
et dans lequel l'un de R1, R2, R3, R4, R5 et R6 n'est ni CH₃ ni H.

24. Composé selon la revendication 22 ou 23, dans lequel R1 n'est pas CH₂-(CH₂-OH)₃-CH₂OH.
- 5 25. Composé selon la revendication 23, dans lequel le R1, R2, R3, R4, R5 ou R6 qui n'est ni H ni CH₃ est R2, R3, R4, R5 ou R6.
- 10 26. Composé selon la revendication 22, dans lequel R1 est -CH₂-(CH₂-OH)₃-CH₂OH.
- 15 27. Composé selon la revendication 22 ou 23, dans lequel R3 et R6 sont H.
- 20 28. Composé selon la revendication 19, dans lequel au moins l'un de R1, R2, R3, R4, R5 et R6 contient un halogène choisi dans le groupe constitué du chlore, du brome et de l'iode.
- 25 29. Composé selon la revendication 28, dans lequel au moins l'un de R1, R2, R3, R4, R5 et R6 est -(CH₂)_n-X où n est 1 ou 2, et X est un halogène choisi dans le groupe constitué du chlore, du brome et de l'iode.
- 30 30. Composé selon la revendication 28, dans lequel au moins l'un des R1, R2, R3, R4, R5 et R6 halogénés est -NR(CH₂)_n-X où R est l'hydrogène ou alkyle à chaîne linéaire constitué de 1 à 6 atomes de carbone, n est un nombre entier de 0 à 6, et X est choisi dans le groupe constitué du chlore, du brome et de l'iode.
- 35 31. Composé selon la revendication 30, dans lequel R4 ou R5 est -NR(CH₂)_n-X, où R est l'hydrogène ou alkyle à chaîne linéaire constitué de 1 à 6 atomes de carbone, n est un nombre entier de 0 à 6 et X est choisi dans le groupe constitué du chlore, du brome et de l'iode.
- 40 32. Composé selon la revendication 18, dans lequel au moins l'un de R1, R2, R3, R4, R5 et R6 est un groupe alkyle ramifié ou non ramifié en C1 à C20, substitué par au moins un groupe -OH.

- 30 33. Composé selon la revendication 18, ayant la structure :



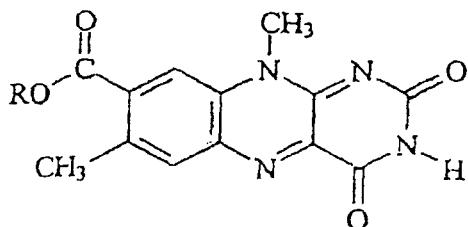
40 dans laquelle R est choisi dans le groupe constitué d'ascorbate, alcool, polyol, amine ou polyamines, saccharides à chaîne linéaire ou cycliques, sulfates, phosphates, polyéthylèneglycols et polyéthers ; ou



50 où R est choisi dans le groupe constitué d'hydrogène et alkyle à chaîne linéaire ou ramifiée éventuellement substitué ayant de 1 à 20 atomes de carbone ; ou

5

(c)

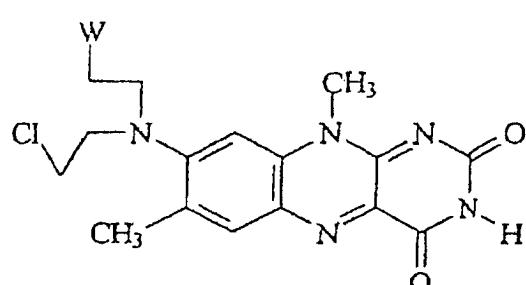


10

où R est choisi dans le groupe constitué d'hydrogène et alkyle à chaîne linéaire ou ramifiée éventuellement substitué ayant de 1 à 20 atomes de carbone ; ou

15

(d)



20

25

où W est choisi dans le groupe constitué d'alcools, polyols, saccharides à chaîne linéaire ou cycliques, amines, polyamines, groupes sulfates, groupes phosphates, groupes ascorbates, chaînes alkyle éventuellement substituées par -OH en une position quelconque, glycols, éthers et de polyéthers, le composé étant soluble dans l'eau à une concentration d'au moins 10 µM.

30

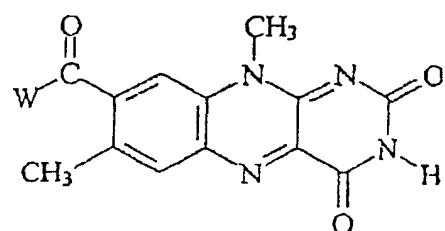
34. Composé selon la revendication 18, dans lequel au moins l'un de R1, R2, R3, R4, R5 et R6 est un agent alkylant.

35. Composé selon la revendication 18, dans lequel au moins l'un de R1, R2, R3, R4, R5 et R6 est un substituant qui rend le composé sensiblement non réactif vis-à-vis de micro-organismes à un pH sensiblement neutre et actif à l'égard de la neutralisation de micro-organismes au pH du fluide biologique.

35

36. Procédé de préparation d'un composé ayant la structure :

40



45

dans laquelle W est un groupe qui rend le composé soluble dans l'eau à une concentration d'au moins 10 µM, comprenant :

50

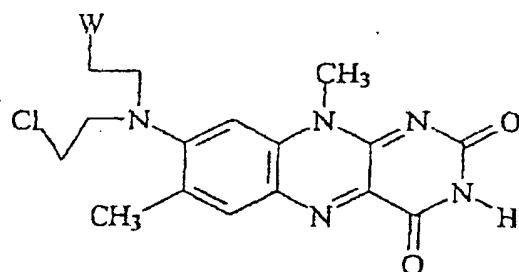
(a) la photolyse de carboxyriboflavine ;

(b) la réaction de (a) avec du chlorure d'oxallyle ;

55

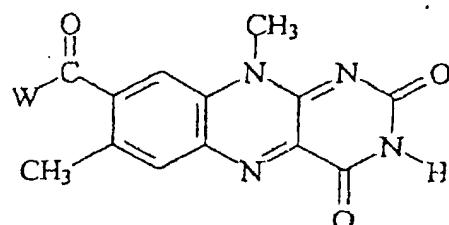
(c) la réaction de (b) avec un élément du groupe constitué d'ascorbate, glucosamine, dérivés de glucose protégés, diéthylèneglycol et triéthylèneglycol.

37. Procédé de préparation d'un composé ayant la structure :



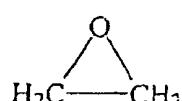
15 dans laquelle W est un groupe qui rend le composé soluble dans l'eau à une concentration d'au moins 10 µM, comprenant :

(a) la mise en contact de



30 avec de l'azoture de sodium ;

(b) la réaction de (a) avec



40 et POCl₃.

(c) la réaction de (b) avec un groupe choisi parmi : alcools, polyols, saccharides à chaîne linéaire ou cycliques, amines, polyamines, groupes sulfates, groupes phosphates, groupes ascorbates, chaînes alkyle éventuellement substituées par -OH en une position quelconque, glycols, éthers et polyéthers.

45

50

55